Allègement du traitement antirétroviral

RIM ABDELMALEK

10/5/2024

Pas de conflit d’intérêt

EPU avec des laboratoires pharmaceutiques

Symposia avec des laboratoires pharmaceutiques

Pandémie

Ralentissement global

Objectifs OMS non atteints

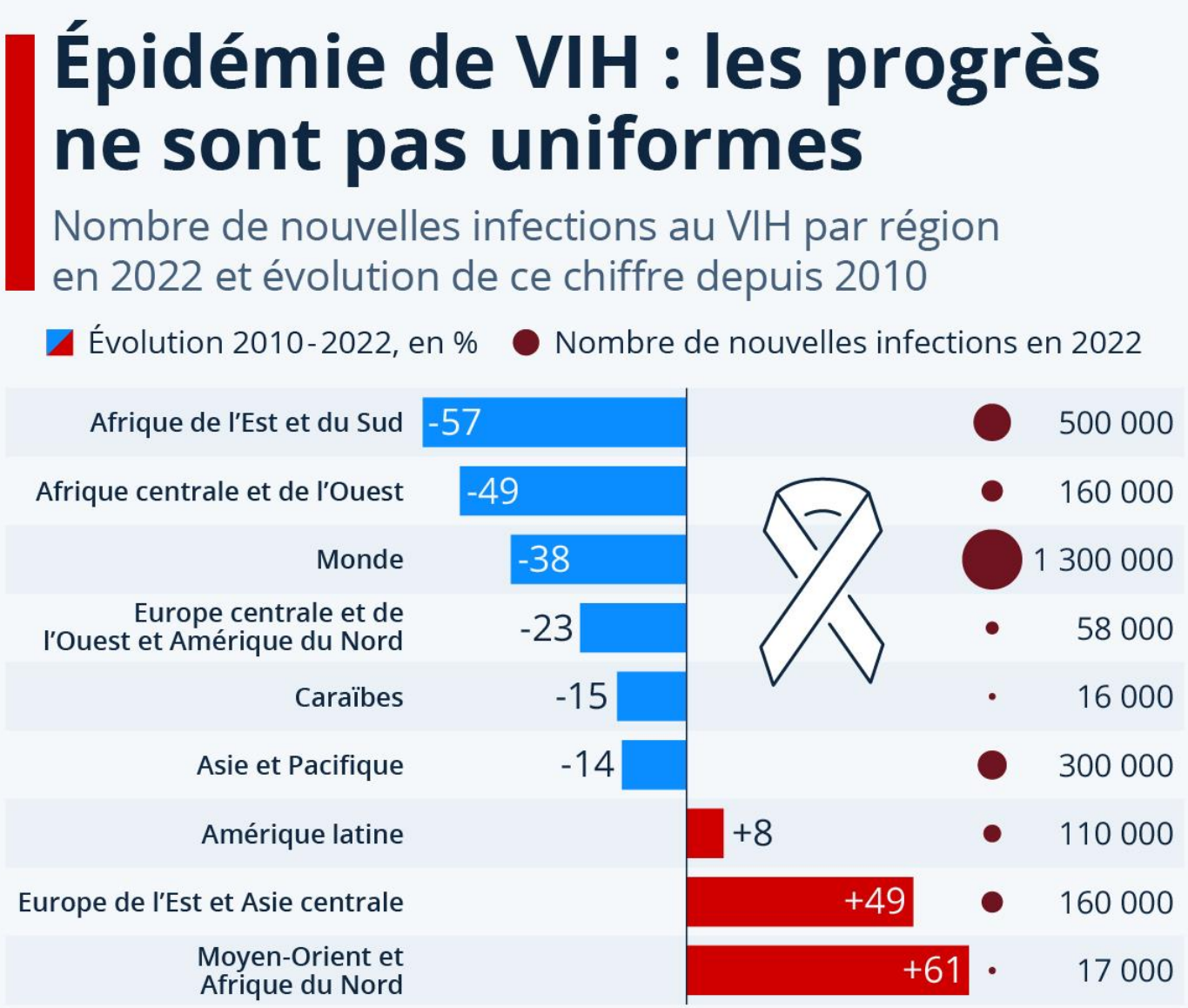
Meilleur accès ARV

Consolider acquis

Autres solutions

- Populations clés
- Personnes instables
- Personnes en difficulté

Allègement ?

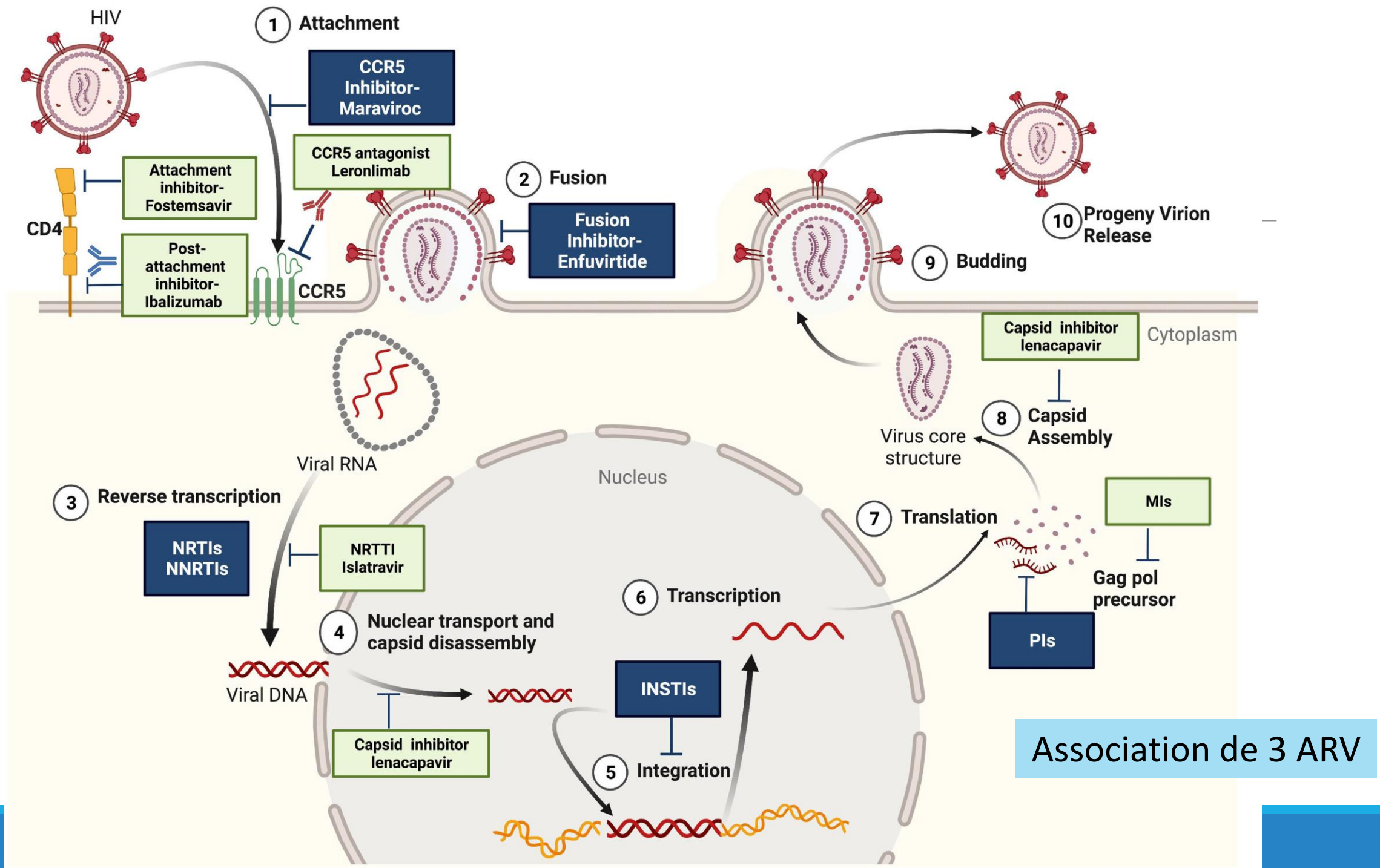


Bases reconnues

VIH

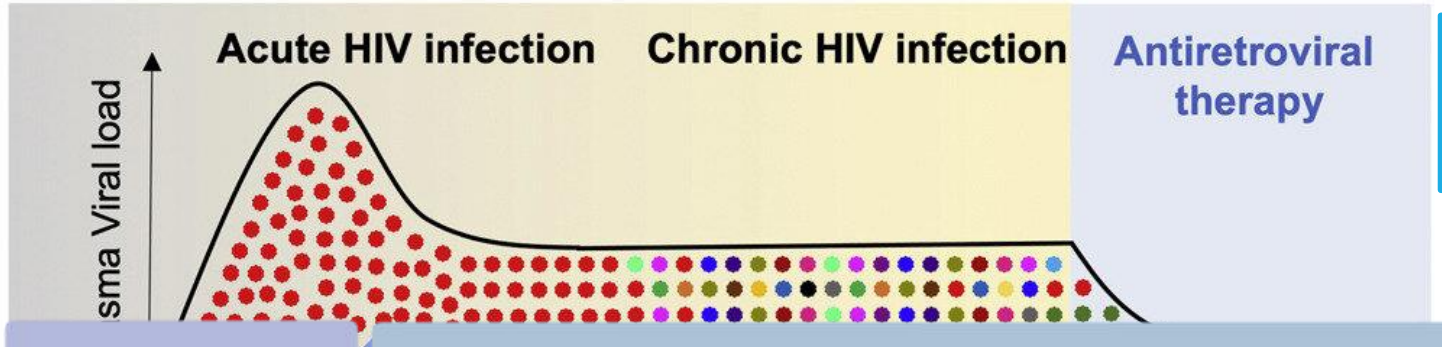
RÉSERVOIR

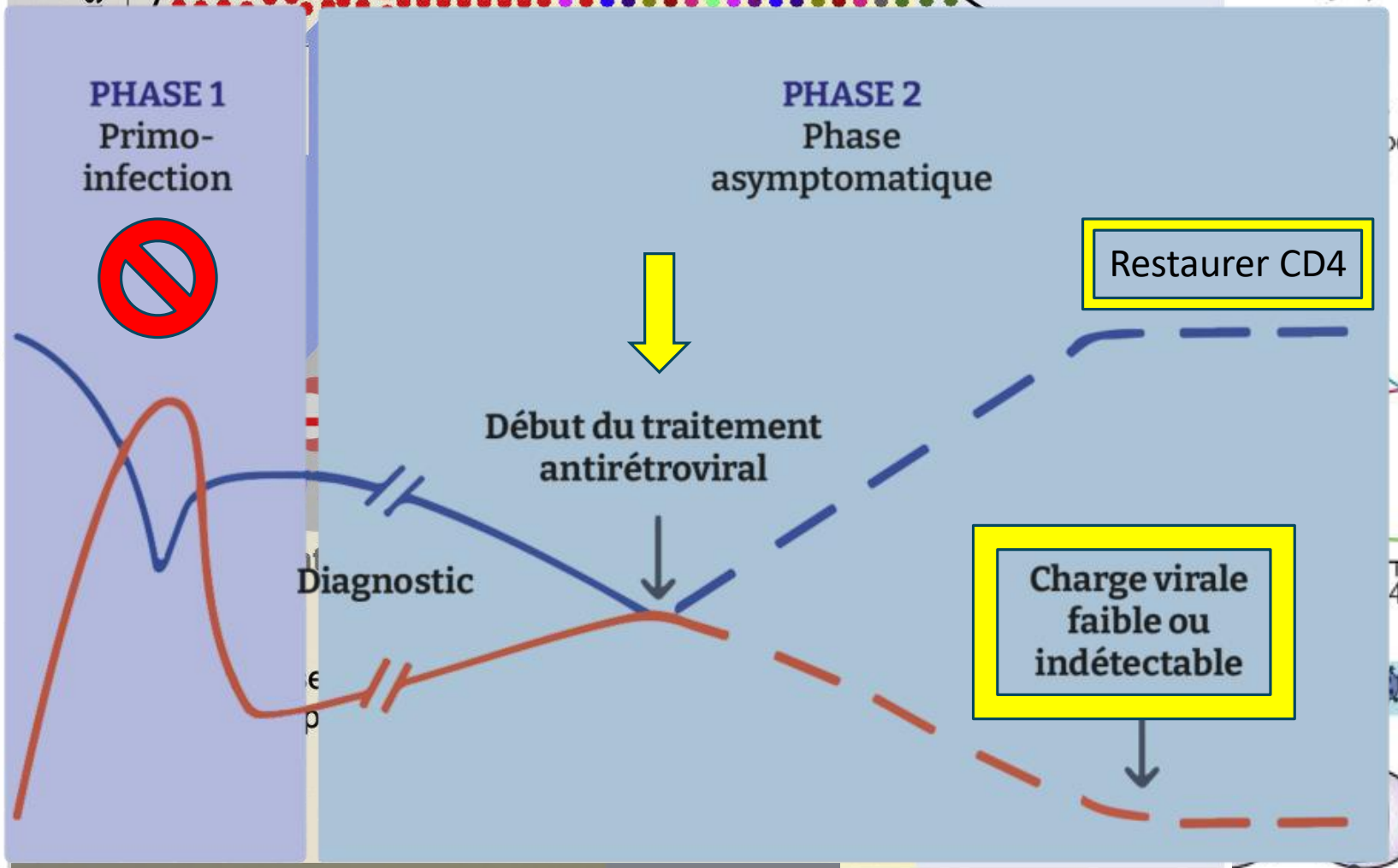
ASSOCIATION ANTIRÉTROVIRAUX

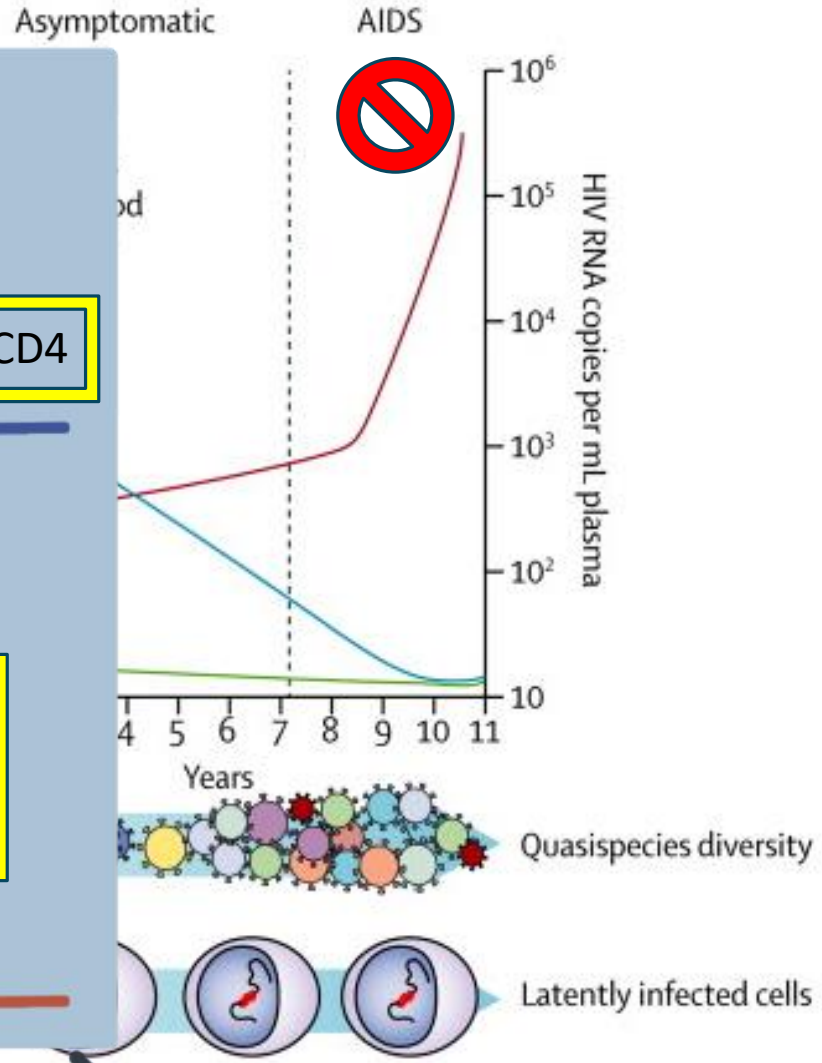


Association de 3 ARV

Action sur le réservoir
Eviter l'inflammation chronique







Immunity (2023). DOI: 10.1016/j.immuni.2023.01.030

A combiner

INTI

Nom	Posologie	
DESCOVY Emtricitabine 200 mg Ténofovir AF 25 mg	Hépatite B 1 1x/jour 30	
DESCOVY Emtricitabine 200 mg Ténofovir AF 10 mg	Hépatite B 1 1x/jour 30	Dose utilisée en présence de *ritonavir* ou *cobicistat*.
KIVEXA Lamivudine 300 mg Abacavir 600 mg	HLA-B*5701 1 1x/jour 30	
TRUVADA Emtricitabine 200 mg Ténofovir DF 300 mg	Hépatite B 1 1x/jour 50	
3TC Lamivudine 300 mg	1 1x/jour	
3TC Lamivudine 150 mg	1 2x/jour	
VIREAD Ténofovir DF 300 mg	Hépatite B 1 1x/jour	
ZIAGEN Abacavir 300 mg	HLA-B*5701 2 1x/jour	
	1 2x/jour	
VEMLIDY Ténofovir AF 25 mg	1 1x/jour 15	Ne peut pas être combiné au *cobicistat* ou *ritonavir*.

IP · IP/ritonavir · IP/cobicistat

Nom	Posologie	
PREZISTA + NORVIR Darunavir 800 mg Ritonavir 100 mg	1 Prezista 1 Norvir 1x/jour	
PREZISTA + NORVIR Darunavir 600 mg Ritonavir 100 mg	1 Prezista 1 Norvir 2x/jour	En présence d'un virus avec au moins 1 mutation et plus, spécifiques au darunavir.
PREZCOBIX Darunavir 800 mg Cobicistat 150 mg	1 1x/jour	
REYATAZ + NORVIR Atazanavir 300 mg Ritonavir 100 mg	1 Reyataz 1 Norvir 1x/jour	
REYATAZ Atazanavir 200 mg	2 1x/jour	
	4 1x/jour	
KALETRA		

Inhibiteurs d'entrée

Nom	Posologie	
CELSENTRI Maraviroc 150 mg	1 2x/jour	La posologie est variable selon la présence d'interactions médicamenteuses : consulter la monographie.
CELSENTRI Maraviroc 300 mg	1 2x/jour	La posologie est variable selon la présence d'interactions médicamenteuses : consulter la monographie.
	2 2x/jour	La posologie est variable selon la présence d'interactions médicamenteuses : consulter la monographie.
RUKOBIA Fostemsavir 600 mg	1 2x/jour	

INI

Nom	Posologie	
ISENTRESS HD Raltégravir 600 mg	2 1x/jour	
ISENTRESS Raltégravir 400 mg	1 2x/jour	
	1 1x/jour	
TIVICAY Dolutégravir 50 mg	1 2x/jour	La posologie 2 fois par jour est recommandée en présence d'un virus avec résistance documentée ou suspectée à l'intégrase ou en présence de certaines interactions médicamenteuses.

INNTI

Nom	Posologie	
ÉDURANT Rilpivirine 25 mg	1 1x/jour	
INTELENCE Étravirine 200 mg	1 2x/jour	
PIFELTRO Doravirine 100 mg	1 1x/jour	
SUSTIVA Éfavirenz 600 mg	1 1x/jour	À prendre au coucher et sans repas gras afin de réduire le risque d'effets secondaires au SNC.
VIRAMUNE Névirapine 200 mg	1 1x/jour	Quatorze premiers jours de traitement : la posologie est de 1 comprimé de 200 mg par jour.
	1 2x/jour ou 2 1x/jour	À la suite des 14 premiers jours de traitement : la posologie est de 200 mg 2 fois par jour ou de 400 mg 1 fois par jour.

Inhibiteur de la capside

Nom	Posologie
SUNLENCA Lenecapavir 927 mg	1 SC 1x/6 mois

Combinaisons fixes

INI/INTI

Nom	Posologie
BIKTARVY Bictégravir 50 mg Emtricitabine 200 mg Ténofovir AF 25 mg	Hépatite B 1 1x/jour 30
GENVOYA Elvitégravir 150 mg Cobicistat 150 mg Emtricitabine 200 mg Ténofovir AF 10 mg	Hépatite B 1 1x/jour 30
STRIBILD Elvitégravir 150 mg Cobicistat 150 mg Emtricitabine 200 mg Ténofovir DF 300 mg	Hépatite B 1 1x/jour 70
TRIUMEQ Dolutégravir 50 mg Lamivudine 300 mg Abacavir 600 mg	HLA-B*5701 1 1x/jour 30
DOVATO Dolutégravir 50 mg Lamivudine 300 mg	1 1x/jour 30

INI/INNTI

Nom	Posologie	
JULUCA Dolutégravir 50 mg Rilpivirine 25 mg	1 1x/jour	
VOCABRIA + ÉDURANT Cabotégravir 30 mg Rilpivirine 25 mg	1 Cabotégravir 1 Rilpivirine 1x/jour	Traitement préliminaire optionel (au moins 28 jours) ou traitement de relais lorsque les injections de Cabenuva n'ont pas pu être administrées dans le délai recommandé.
CABENUVA Cabotégravir 600 mg / 3 ml Rilpivirine 900 mg / 3 ml	1 Cabotégravir 1 Rilpivirine	**1er mois** Une injection intramusculaire de chacun des médicaments dans les muscles fessiers (doses de charge). **2e mois et tous les 2 mois suivants** Une injection intramusculaire de chacun des médicaments dans les muscles fessiers.

IP/INTI

Nom	Posologie
SYMTUZA Darunavir 800 mg Cobicistat 150 mg Emtricitabine 200 mg Ténofovir AF 10 mg	Hépatite B 1 1x/jour 30

INNTI/INTI

Nom	Posologie	
ATRIPLA Éfavirenz 600 mg Emtricitabine 200 mg Ténofovir DF 300 mg	Hépatite B 1 1x/jour 50	À prendre au coucher et sans repas gras afin de réduire le risque d'effets secondaires au SNC.
COMPLERA Rilpivirine 25 mg Emtricitabine 300 mg Ténofovir DF 300 mg	Hépatite B 1 1x/jour 50	
DELSTRIGO Doravirine 100 mg Lamivudine 300 mg Ténofovir DF 300 mg	Hépatite B 1 1x/jour 50	
ODEFSEY Rilpivirine 25 mg Emtricitabine 200 mg Ténofovir AF 25 mg	Hépatite B 1 1x/jour 30	

Disponibilité en Tunisie ?

INTI	INNTI	IP	INI	IE	Boost
AZT 300 DDI D4T **3TC 150** FTC **ABC 300** **TDF 300** TAF	NVP **EFV 200, 400** ETR RPV DRV	SQV IDV NFV APV FPV TPV **LPV/r 200/50, 100/25** **ATV/r 300/100** **DRV 600**	EVG RAL 400 **DTG 50, 10** BIC CTG	ENF MVC FTR Anticorps	**RTV 100** Cob

Formes combinées			
AZT/3TC 600/300, 60/30 AZT/3TC/ABC **ABC/3TC 600/300, 120/60** **TDF/FTC 300/200**	TDF/FTC/EFV **TDF/3TC/EFV 300/300/400** TDF/FTC/RPV TAF/FTC/RPV TDF/3TC/DOR **TDF/3TC/DTG 300/300/50**	TDF/FTC/EVG/cob TAF/FTC/EVG/cob ABC/3TC/DTG TAF/FTC/BCG	RPV/DTG 3TC/DTG TAF/FTC TAF/FTC/DRV DRV/cob

Causes d’arrêt des ARV?

Effets indésirables

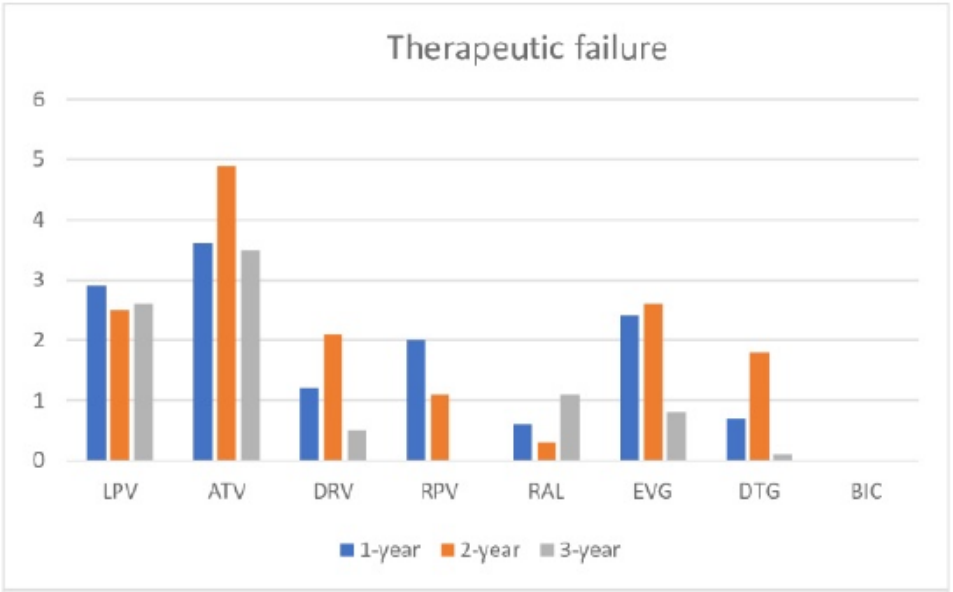
- Digestifs
- Neuro-psychiatriques
- Complications cardio-vasculaires

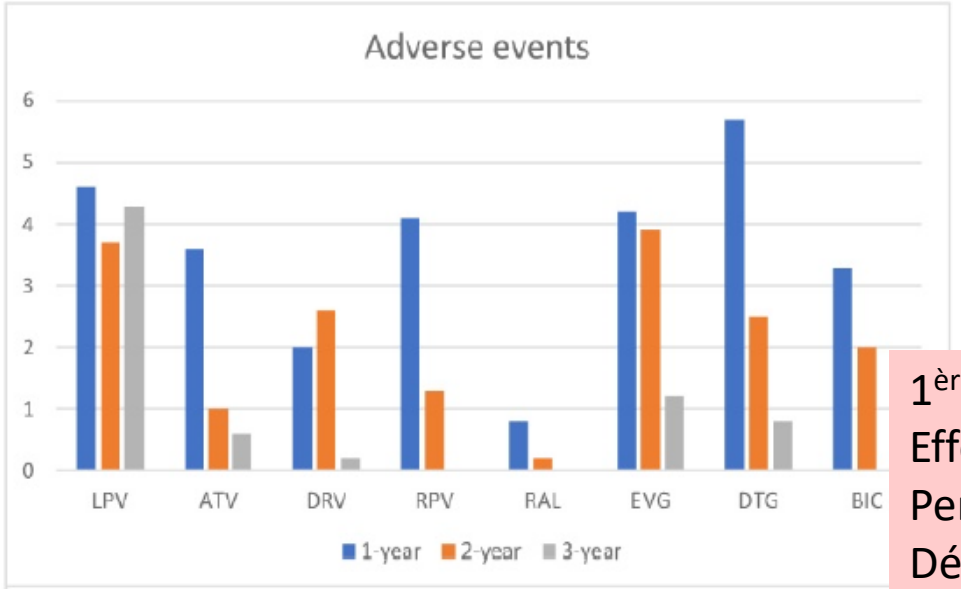
Nombre de comprimés

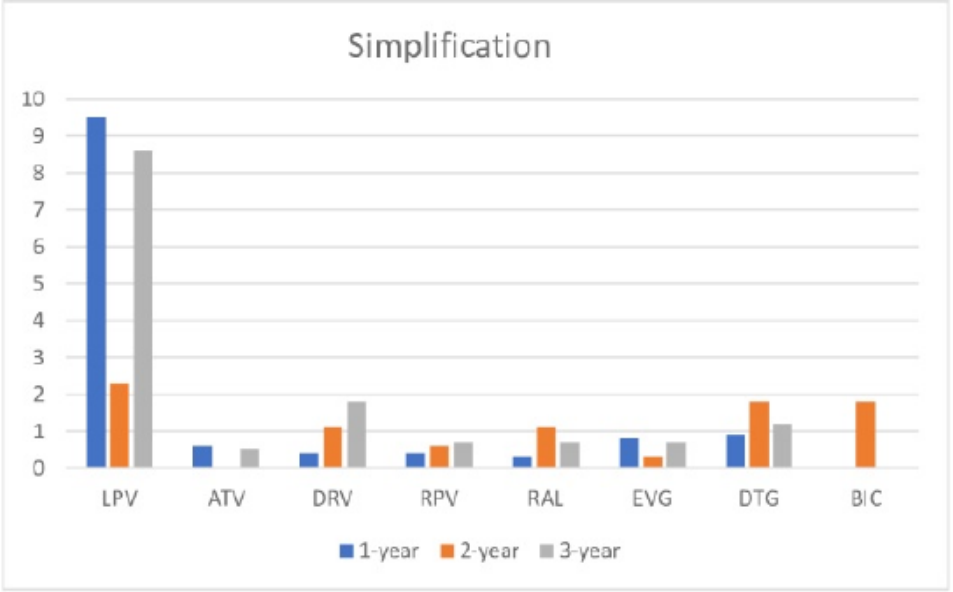
Addictions

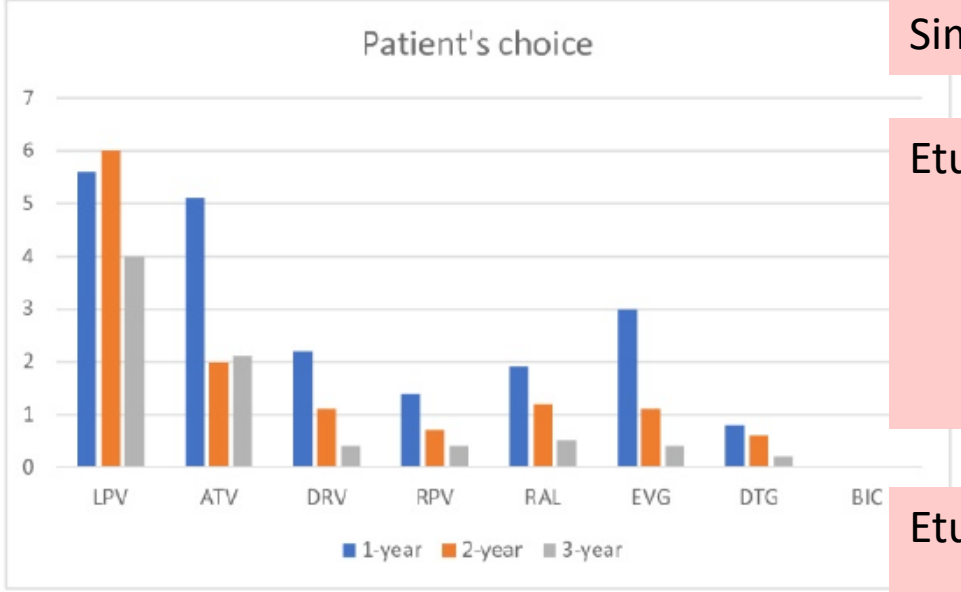
Conditions sociales difficiles

Stigmatisation









4400 PVVIH
Rétrospective
20 ans 2002-22

1ère année, causes
Effets indésirables : 3,8%
Perte de vue : 3,7%
Décision du patient : 2,6%
Simplification : 1,3%

Etude multivariée, prétraités
- LPV, ATV, RPV, EVG/c
- CD4 < 250 c/µl
- UDI
- VHC

Etude multivariée, naïfs
- LPV/r

Figure 1. Percentage of discontinuation causes in patients enrolled in the SCOLTA project cohorts during the first, second and third year of treatment.

Current HIV/AIDS
https://doi.org/10.

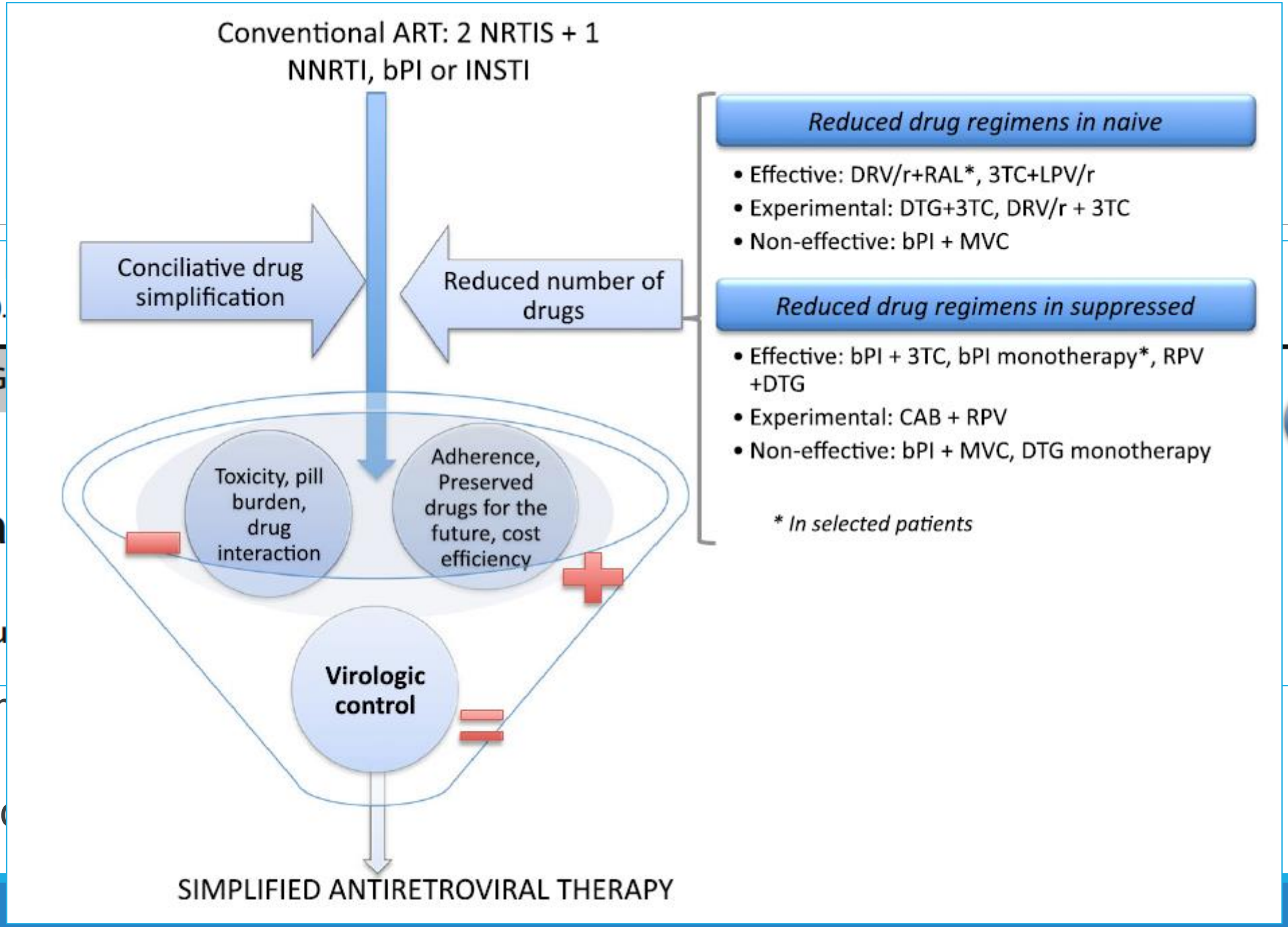
HIV PATHOG

New Stra

Rosa de Migu

Dir

Réc

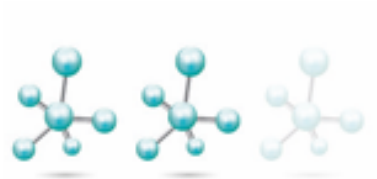


CrossMark

Moyens de l’allègement

Moins de médicaments

- 2 molécules
- 7 jours/7



Moins de prises par semaine

- 3 molécules
- 4 jours/7

Moins de comprimés à chaque prise

- 1 comprimé combiné
- 2 comprimés

Injectable longue demi-vie

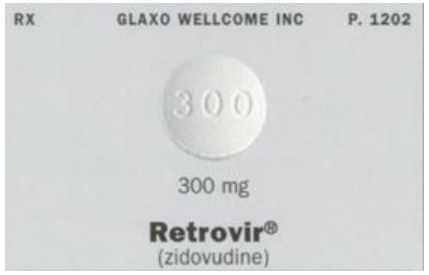
- Nombre de comprimés

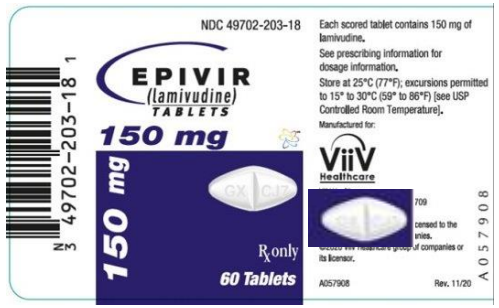
- Nombre de jours

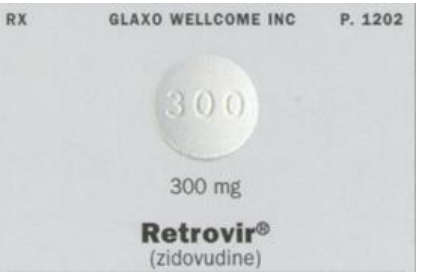
- Un ou deux médicaments

- Injectables longue durée

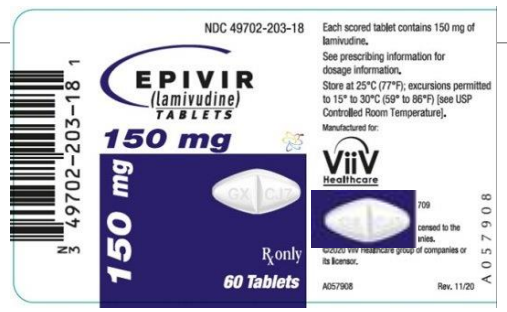
Il était une fois! The pill burden

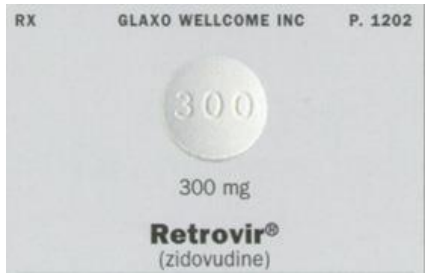




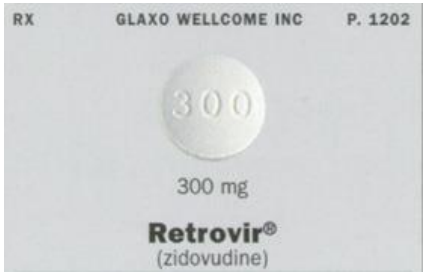


Première simplification

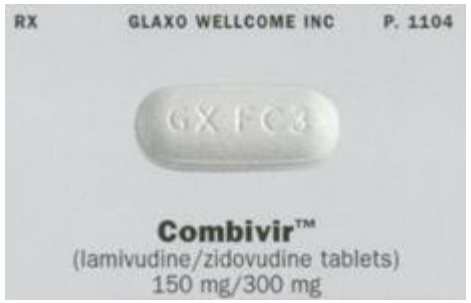




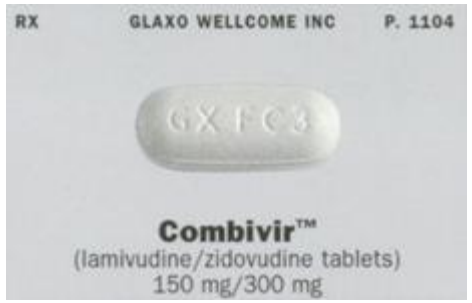
Deux prises/jour
Boost efficace

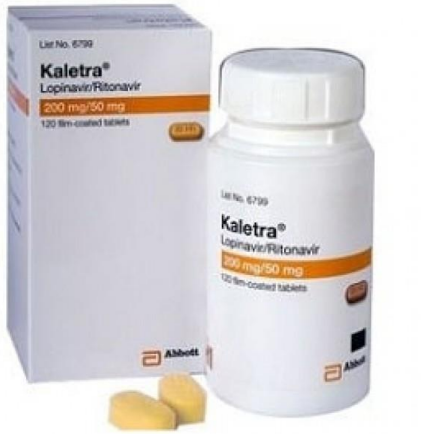


Puis vinrent les associations fixes !



Effets indésirables



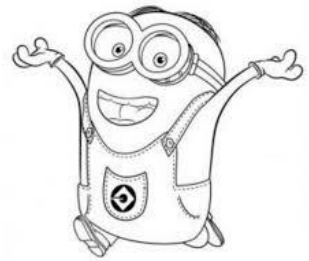


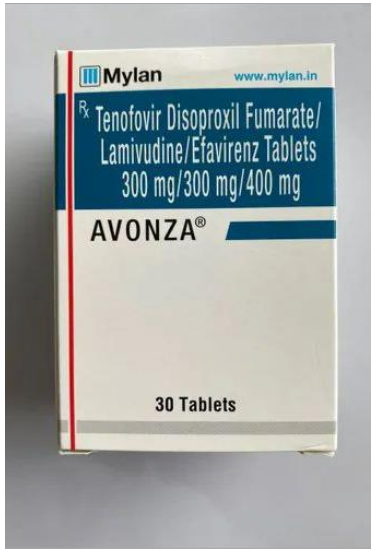
Puis une fois par jour

Effets indésirables

Inhibiteur d’intégrase!

Et enfin la pilule unique !





Observance meilleure
Effets indésirables moindres

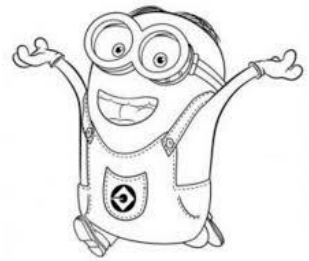
Génériques ?

Table 2. Physicians' opinions about effectiveness, safety and costs of generic ARVs, and needs for information about them

	CA	A	AD	D	CD
If we change from a branded antiretroviral drug to its generic equivalent, *keeping the number of daily pills and the number of doses constant*, I think that:					
treatment adherence will decrease	0 (0.0)	1 (0.6)	8 (4.7)	64 (37.9)	96 (56.8)
there will be more adverse effects	0 (0.0)	13 (7.7)	25 (14.8)	76 (45.0)	55 (32.5)
virological failure will be more likely	0 (0.0)	6 (3.6)	17 (10.1)	66 (39.1)	80 (47.3)
the patient will need more frequent clinical follow-up	2 (1.2)	13 (7.7)	14 (8.3)	63 (37.3)	77 (45.6)
the cost for the healthcare system will be lower	85 (50.3)	67 (39.6)	13 (7.7)	2 (1.2)	2 (1.2)
If we change from a combination of antiretrovirals as an STR to its separate equivalent generic components (breaking the fixed-dose combination), I think that:					
treatment adherence will decrease	37 (21.9)	71 (42.0)	33 (19.5)	24 (14.2)	4 (2.4)
there will be more adverse effects	5 (3.0)	27 (16.0)	45 (26.6)	59 (34.9)	33 (19.5)
virological failure will be more likely	8 (4.7)	63 (37.3)	33 (19.5)	53 (31.4)	12 (7.1)
the patients will need more frequent clinical follow-up	10 (5.9)	36 (21.3)	44 (26.0)	52 (30.8)	27 (16.0)
the cost for the healthcare system will be lower	56 (33.1)	69 (40.8)	26 (15.4)	16 (9.5)	2 (1.2)
Regarding your needs to be informed about generic antiretroviral drugs:					
I need more information about the *effectiveness and safety* of generic antiretroviral drugs	37 (21.9)	60 (35.5)	26 (15.4)	35 (20.7)	11 (6.5)
I need more information about the *price difference* between generic and branded antiretroviral drugs	55 (32.5)	68 (40.2)	22 (13.0)	20 (11.8)	4 (2.4)
I think we need consensus-based clinical guidelines for physicians and pharmacists for the prescription of generic antiretroviral drugs	42 (24.9)	75 (44.4)	32 (18.9)	17 (10.1)	3 (1.8)

Values are *n* (%).
CA, completely agree; A, agree; AD, neither agree nor disagree; D, disagree; CD, completely disagree.

Et enfin la pilule unique !



Observance meilleure
Effets indésirables moindres

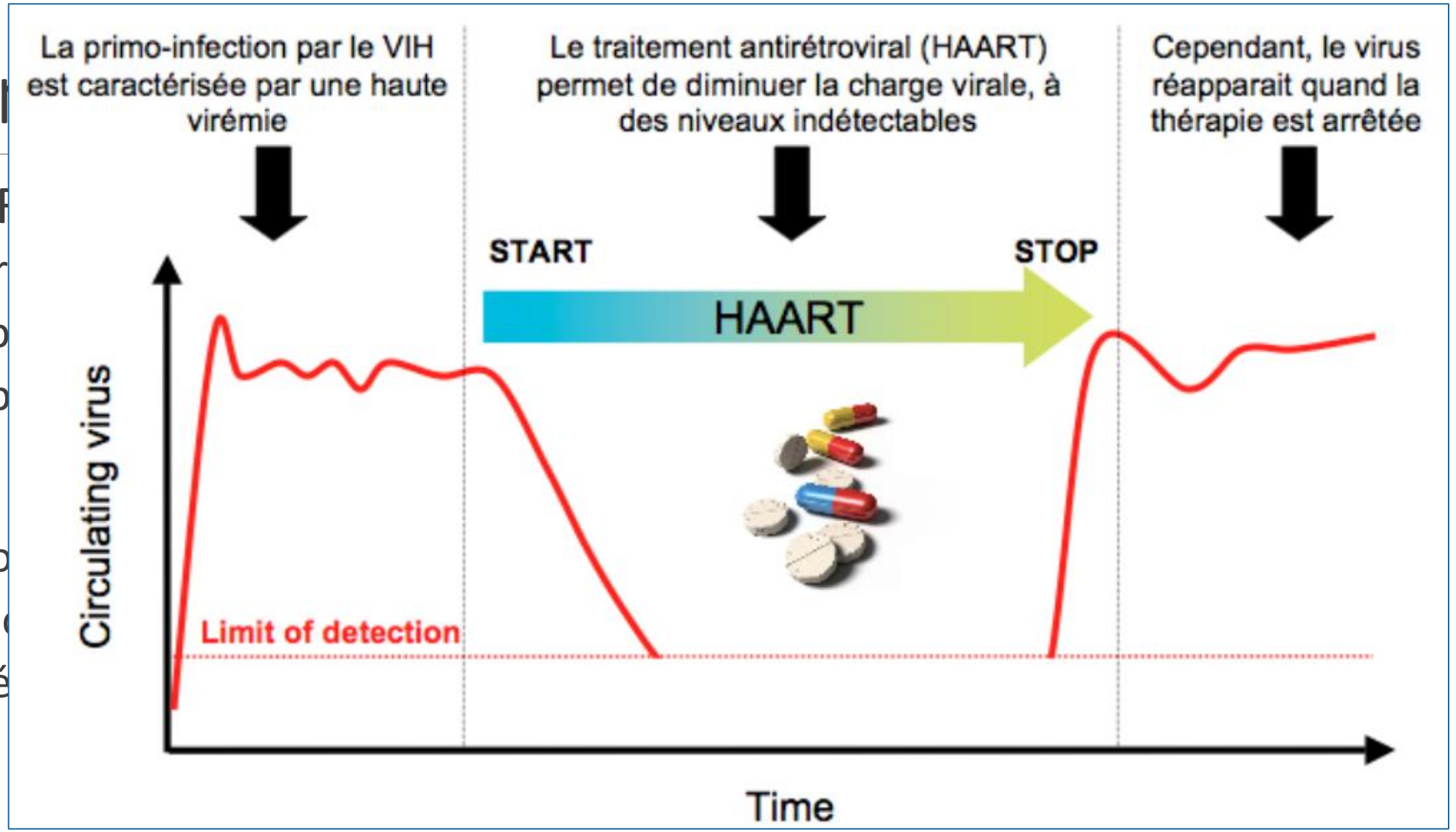
A quand la prochaine simplification?

Dilemm

Objectif AR
- Maintenir
- Éviter blip
- Eviter app

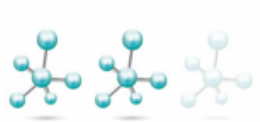
Moyens
- Associatio
- Observanc
- Dosage sé

Comment



- Nombre de comprimés

- Nombre de jours



- Un ou deux médicaments

- Injectables longue durée

Table 1. Pilot studies of intermittent antiretroviral treatment

Study	Authors	Year	Study design	Total patients included (test/control)	Inclusion criteria	Exclusion criteria	CD4+ count	Cycle on/off	ART group test N (%)	VL undetect. duration (years)	Outcome
FOTO[11]	Calvin J. Cohen, Amy E. Colson, Alexander G. Sheble-Hall, et al.	2007	Open-label, single-arm, prospective pilot study	30	HIV 1 infection CD4 + > 200/mm ≥ VL undetectable for ≥ 3 months Treatment with stable ART combination PI-treated patients with virological failure on prior PI-based regimen admitted	NNRTI-based regimen with previous virological failure on prior NNRTI-based regimen	612	5/2	Efavirenz-based (10) PI-based (10) Nevirapine-based (10) 70% : Not first line ART	≥ 3 months	48 weeks : Undetectable rate; Efavirenz: 100% Nevirapine: 89% PI: 78%
Reynolds et al. 2010[12]	Steven J. Reynolds, Cissy Kityo, Claire W. Hallahan, et al.	2010	RCT, non-inferiority	146 (32 (7/7)/ 57 (5/2)/ 57)	– CD4+ ≥ 125 c/mm ≥ – VL <50 c/mL		264	7/7 5/2	ART including Boosted PI based ART (1.8%) or Efavirenz-based ART (98%) If nevirapine; switch to PI or Efavirenz	48 sem (ART exposition)	**72 weeks** ART failure (VL ≥ 10.000 c/mL or > 1.000 c/mL on 2 measurements or > 400c/mL at the end of the study) **7/7 arm: 31% >> Stopped** 5/2 arm: 11.5% Continuous arm: 21.6% CD4 + count (decrease > 30%) 5/2: 1 not statistically different Adverse events (AE): Reduction of lipodystrophy and lactic acidoses

Table 1. Pilot studies of intermittent antiretroviral treatment *(Continued)*

Study	Authors	Year	Study design	Total patients included (test/control)	Inclusion criteria	Exclusion criteria	CD4+ count	Cycle on/off	ART group test N (%)	VL undetect. duration (years)	Outcome
Leibowitch et al. 2010[13]	Jacques Leibowitch, Dominique Mathez, Pierre de Truchis, et al.	2010	Single arm, prospective	48 (39) (12)	Selection on the basis on the volunteering's patient and adherence to repeated monitoring		154 ± 82	5/2 et 4/3 (3/4) (2/5)	Backbone NRTI: 91% emtricitabine+tenofovir disoproxil + 32.4% Efavirenz 35.6% Boosted PI 1.3% INI Triple NRTI backbone (Didanosine +lamivudine+tenofovir disoproxil) + NNRTI: 20.4% NNRTI: 56.5% Boosted PI: 40.4%	5.5 ± 2.8 (ART exposition)	Virological failure (VL > 50 c/mL): 5/2: 0/48 (56w) 4/3: 0/47 (84w) 3/4: 4/39 (50w) 2/5: 2/12 (24w)
ICCARE[14]	Jacques Leibowitch, Dominique Mathez, Pierre de Truchis, et al.	2015	Single-arm, prospective	94 (84) (66) (12)	– Written informed consent – Tri ou quadritherapy 7 days/7 – VL < 50 c/mL for ≥ 5 months		181 ± 98	4/3 (3/4) (2/5) (1/6)	2 NRTI (emtricitabine, tenofovir, abacavir, or didanosiene) + [Boosted PI (Lopinavir, atazanavir, darunavir or amprenavir) or NNRTI (Evafirenz, nevirapine, or etravirine)] OR Combinaisons 3 NRTI+NNRTI OR Others combinations : i. Raltegravir + etravirine+boosted PI ii. 2-3 NRTI + etravirine iii. LPV/r + didanosine	6.3±4 (ART exposition)	87 weeks; virological failure rate: 4/3: 0% 3/4: 11.9% 2/5 10.6% 1/6: 8.3% Raltegravir-based treatment given 3 days/4: 87% virological failure

Table 2. Recent studies of intermittent antiretroviral treatments.

Study	Authors	Year	Study design	N total patients included (test/ control)	Inclusion criteria's	Exclusion criteria's	CD4 + count	Cycle on/off	ART group test n (%)	VL undetect. duration (years)	Outcome
BREATHER (PENTA16)[19]	Karina Butler, Jamie Inshaw, Deborah Ford, et al	2016	Randomized, controlled, non-inferiority trial	199 (99/100)	– HIV 1 infected peoples – 8–24 years – CD4 ≥ 350 cells/mm ≥ – VL < 50 c/mL for ≥ 12 months – Efavirenz based ART – VL blips > 50 and < 1000 c/mL can be enrolled – Assay that detect RNA VL ≥ 50 c/mL – 1st line ART regimen – Efavirenz based TAR+2 NRTI for 12 months	– Pregnancy (or risk) – Acute illness – Concomitant therapy for an acute illness – Creatinine or liver enzymes elevation (Grade 3 or above) – Nevirapine or boosted PI regimen – Previous ART monotherapy (except for prevention of mother–to–child transmission)	793	5/2	Efavirenz – based ART + Zidovudine/ lamivudine 52 (53) or Tenofovir, lamivudine/ emtricitabine 25 (25) or Abacavir, lamivudine/ emtricitabine 22 (22)	12 months min.	48 weeks: No significative difference about: – Virological failure (VL > 50 cop/mL); 1.2% – Resistance acquisition – CD4 count – AE
BREATHER extended follow–up[20]	Anna Turkova, Cecilia L. Moore, Karina Butler, et al	2017	Randomized, controlled, non-inferiority trial	BREATHER 199 (99/100)	– HIV 1 infected peoples – 8–24 years – CD4 ≥ 350 cells/mm ≥ – VL < 50 c/mL for ≥ 12 months – Efavirenz based ART	– Pregnancy (or risk) – Acute illness – Concomitant therapy for an acute illness – Creatinine or liver enzymes elevation (Grade 3 or above)	350–500 14% > 500 86%	5/2		12 months min 6.1 (ART exposition)	96 et 144 weeks: No significative difference about: – Virological failure; 2% – AE – CD4+count – Mutations
ANRS 162–4D trial[21]	Pierre de Truchis, Lambert Assoumo, Roland Landman, et al.	2017	Single–arm, prospective multicenter trial	100	– HIV 1 infected peoples – ≥ 18 ans – ART for ≥ 12 months – VL ≤ 50 c/mL for ≥ 12 months – No genotype resistance – CD4+ > 250 for ≥ 6 months – ART: 2 NRTI + PI boosté (darunavir, lopinavir, and atazanavir) ou NNRTI (efavirenz, rilpivirine, etravirine)		665	4/3	Efavirenz: 40 (40) Rilpivirine: 26 (26) Etravirine: 5 (5) Darunavir/ritonavir: 15 (15) Atazanavir/ritonavir: 13 (13) Lopinavir/ritonavir: 1 (1)	4 5.1 (ART exposition)	48 weeks: 96% VL < 50 copies/mL 4 viral blips: Rilpivirine (2) Atazanavir/ ritonavir Lopinavir/ ritonavir

Table 2. Recent studies of intermittent antiretroviral treatments *(Continued)*

Study	Authors	Year	Study design	N total patients included (test/ control)	Inclusion criteria's	Exclusion criteria's	CD4 + count	Cycle on/off	ART group test n (%)	VL undetect. duration (years)	Outcome
ANRS 162–4D trial[21]					– No change in ART regimen in the previous 4 months – laboratory tests: GFR > 60mL/min, AST-ALT 3x ULN (upper limit of normal), Hb > 10g/dL, platelets> 100.000/mm^3 – Pregnancy test negative, contraception during the study – Written informed consent						
QUATUOR[22]	R. Landman, P. De Truchis, L. Assoumou, et al (ANRS - France)	2019	Randomized, open-label controlled, multicenter, non-inferiority trial	636 (318/318)	– VL < 50 copies/mL for ≥ 12 months – No genotype resistance – CD4 > 250 cells/mm^3 – PI-, NNRTI- ou INI- based regimen with a 2 NRTI backbone	– No complete genotype or resistance – No virological criteria	689	4/3	Tenofovir disoproxil or tenefovir alafenamide/ emtricitabine 230 (72.3) abacavir/lamivudine 88 (27.7) INI (dolutegravir/ elvitegravir/ raltegravir) 152 (47.8) (73/65/14) NNRTI (rilpivirine/ efavirenz/etravirine) 148 (46.5) (118/24/6) PI (darunavir/ atazanavir/lopinavir) 18 (5.7) (16/2/0)	5.1	48 weeks: No significative difference about: – Virological failure: 0.6% – Adverse events (AE) – Deaths

Pas de risque sur le réservoir?

Faut-il quantifier le réservoir?

Durée plus longue > 96 semaines

INNTI T1/2 longue

IP T1/2 cellulaire longue
T1/2 liaison longue

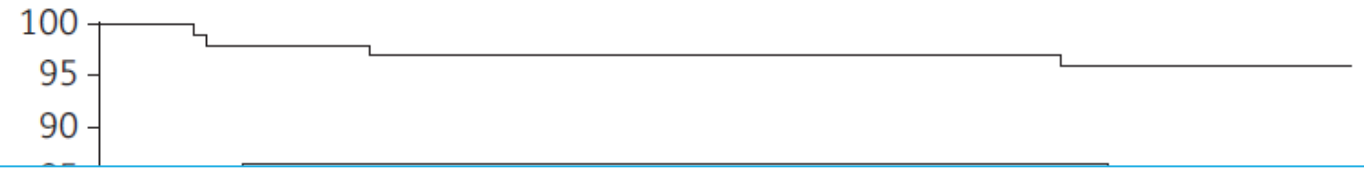


Table 4. Drug concentrations: mean values off and on therapy for each drug (ng/mL)

Antiretroviral	*n*	'ON', mean (SD)	'OFF', mean (SD)	Δ(OFF − ON), mean (SD)	Percentage of change Δ(OFF − ON)/ON, mean (SD)	*P*
Efavirenz	38	2218 (1046)	692 (391)	−1526 (781)	−69% (10)	<0.0001
Etravirine	5	447 (360)	269 (266)	−179 (101)	−47% (11)	0.0625
Rilpivirine	26	106 (51)	39 (20)	−66 (40)	−63% (13)	<0.0001
Atazanavir	12	1087 (644)	52 (146)	−1035 (637)	−96% (11)	0.0005
Darunavir	15	2587 (1393)	17 (18)	−2570 (1382)	−99% (0)	<0.0001
Lopinavir	1	3922	0	−3922	−100%	

Limits of quantification: <20 ng/mL for darunavir, atazanavir and lopinavir; <100 ng/mL for efavirenz; <10 ng/mL for etravirine; and <5 ng/mL for rilpivirine.
Efficacy cut-offs: darunavir >2000 ng/mL; atazanavir >200 ng/mL; lopinavir >4000 ng/mL; efavirenz >1000 ng/mL; etravirine >50 ng/mL; and rilpivirine >40 ng/mL.
The time between the last medication intake and sample collection was considered as 'off period' if ≥48 h and as 'on period' if <48 h. For each participant and each drug, we calculated the mean of all measurements during the 'on period' ('ON') and all measurements during the 'off period' ('OFF'). The Wilcoxon paired test was used to compare changes in residual antiretroviral concentrations between 'ON' and 'OFF'.

Figure 2. Probability of therapeutic success (Kaplan–Meier). Data for one patient were excluded at week 12 because of study treatment discontinuation due to pregnancy.

J Antimicrob Chemother. 2024 Apr 24:dkae112. doi: 10.1093/jac/dkae112. Online ahead of print.

Plasma concentrations of antiretroviral drugs in a successful 4-days-a-week maintenance treatment strategy in HIV-1 patients (ANRS 170-Quatuor trial)

Emuri Abe [1], Roland Landman [2 3], Lambert Assoumou [4], Karine Amat [3], Sidonie Lambert-Niclot [5], Jonathan Bellet [4], Séverine Gibowski [6], Pierre-Marie Girard [7], Laurence Morand-Joubert [5], Pierre de Truchis [8], Jean-Claude Alvarez [1]

Affiliations + expand

PMID: 38656448 DOI: 10.1093/jac/dkae112

Pas d'impact sur
- Résistances/mutations
- CVP

Conclusions

The 4/7-day treatment option led to antiretroviral blood levels close to continuous treatment after the four consecutive days of medication, and to low levels at the end of the non-treatment period.

Four days/week antiretroviral maintenance strategy (ANRS 170 QUATUOR): substudies of reservoirs and ultrasensitive drug resistance

Get access >

Journal of Antimicrobial Chemotherapy, Volume 78, Issue 6, June 2023, Pages 1510–1521,
https://doi.org/10.1093/jac/dkad119

Conclusions

These findings support the potency of a 4/7 days maintenance strategy on virological suppression at the reservoirs and emergent resistance level, including minority variants.

33 patients

100% CVP < 50
CD4 maintenus
Satisfaction PVVIH

Age > 18 ans
ARV > 12 mois
2 INTI + rilpivirine
CVP < 50 copies/ml > 12 mois
CD4 > 200/µl > 6 mois
Pas de résistances

Journal of Antimicrobial Chemotherapy

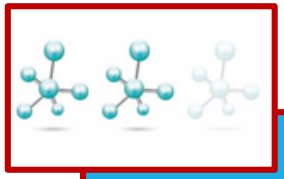
Short-cycle therapy in HIV-infected adults: rilpivirine combination 4 days on/3 days off therapy

Table 2. Data on rilpivirine concentration

	Number of samples	Concentration (ng/mL), median (IQR)	Samples <50 ng/mL, *n* (%)
Week 4	29	6.4 (0–49.2)	22 (75.9)
Week 8	27	0 (0–38.3)	22 (81.5)
Week 12	29	32.8 (12.2–88.6)	20 (68.9)
Week 24	30	34.7 (23.65–65.8)	18 (60)
Total	115	24.7 (0–60.35)	82 (71.3)

- Nombre de comprimés

- Nombre de jours



- Un ou deux médicaments

- Injectables longue durée

EXPERT OPIN
https://doi.or

REVIEW

Curren
ART-ex

Barbara F

[a]Infectious
Diseases, C
Siena, Italy

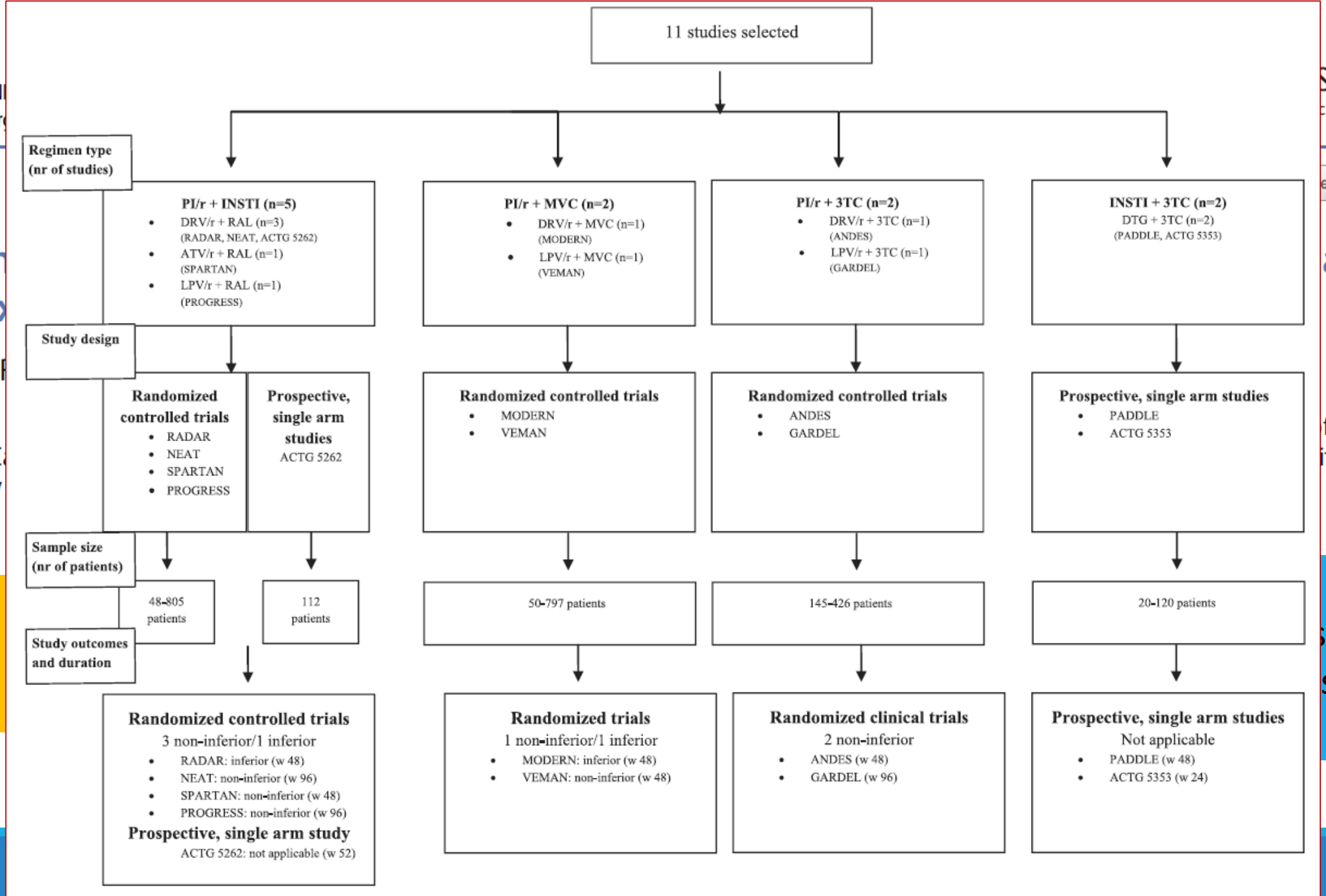
& Francis
cis Group

eck for updates

and

f Infectious
ity of Siena,

s/ml
s



Open Forum Infectious Diseases

BRIEF REPORT

192 PVVIH naïfs
2013-2018
Génotypage de résistance

nt Si
With 2-Drug Regimens: Im
Transmitted Drug Resistan

Génotypage initial

Etude épidémiologie

[1]Research Unit Molecular Diagnostics, Diagnostic and Research
Biomedicine, Medical University of Graz, Graz, Austria, [2]Divisior

Résistances transmises 15,6%
> 50% résistances en foyers
2% non éligibles pour 1 ou 2 molécules

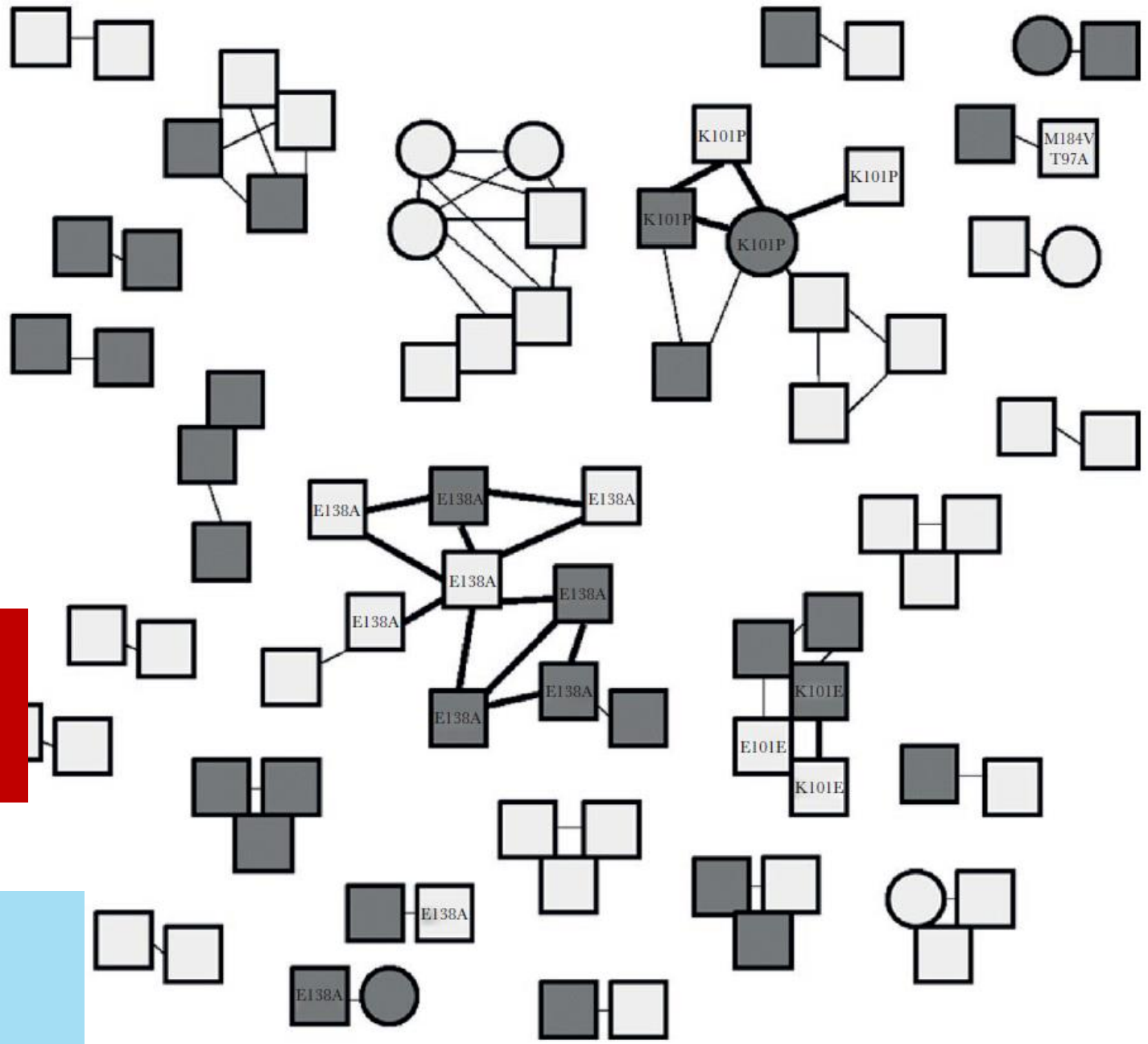
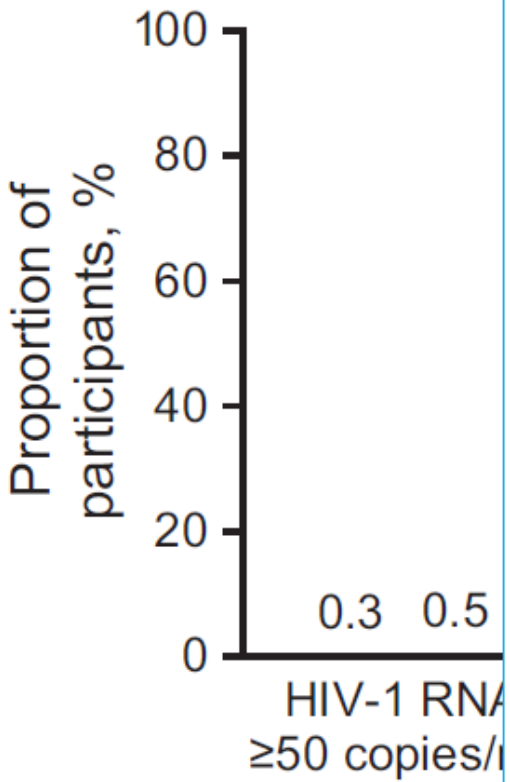


Figure 1. Transmission network analysis: 82 genetically linked individuals forming 26 clusters. Dark gray circles and squares, antiretroviral therapy (ART)–naïve residents of Southeast Austria with newly diagnosed HIV-1 infection 2013 through 2015; light gray circles (females) and squares (males), ART-naïve residents of Southeast Austria with newly diagnosed HIV-1 infection 2016 through 2018; bold lines, shared drug resistance mutations.

Clinical Infectious Dis

MAJOR ARTI



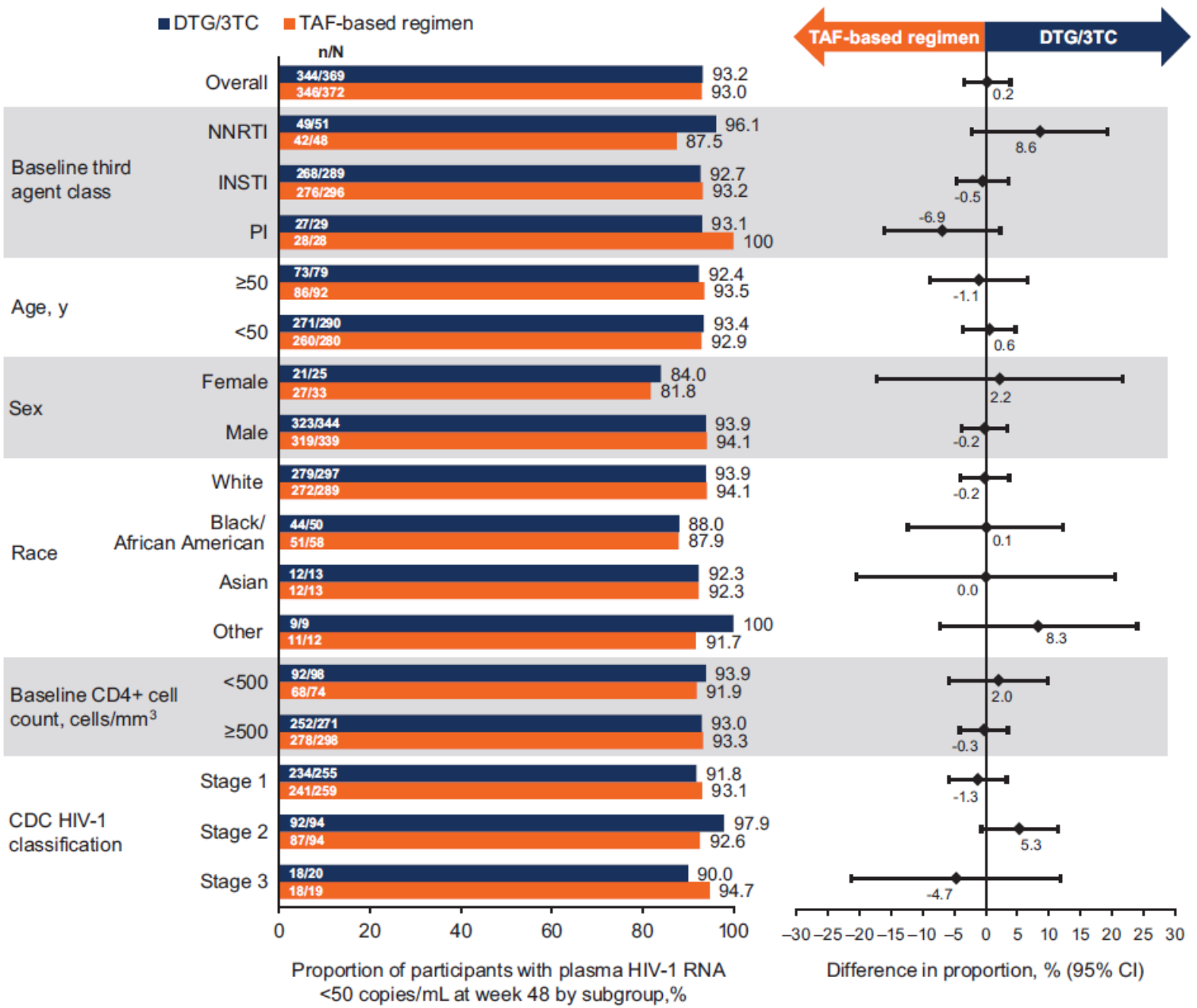


Figure 3. Proportion of participants with HIV-1 RNA <50 copies/mL at week 48 by subgroup in the intention-to-treat–exposed study population (US Food and Drug Administration Snapshot algorithm). Abbreviations: 3TC, lamivudine; CDC, Centers for Disease Control and Prevention; CI, confidence interval; DTG, dolutegravir; HIV-1, human immunodeficiency virus type 1; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide.

hivma
iv medicine association
OXFORD

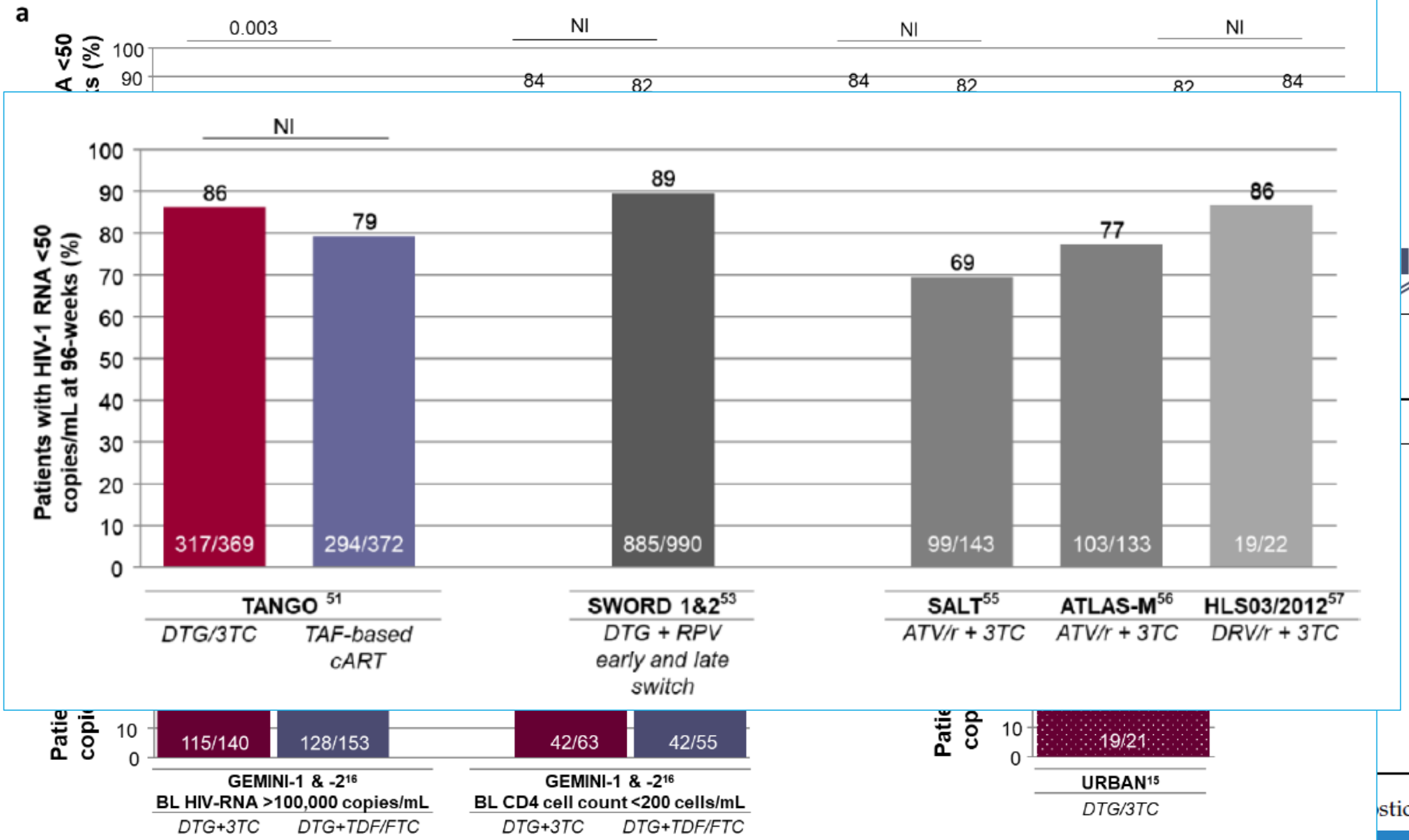
	DTG/3TC (N = 369)	TAF-based regimen (N = 372)
	344 (93.2)	346 (93.0)
	1 (0.3)	2 (0.5)
	0	2 (0.5)
	1 (0.3)	0
	24 (6.5)	24 (6.5)
	12 (3.3)	1 (0.3)
	12 (3.3)	22 (5.9)
	0	1 (0.3)

**Mounir Ait-Khaled,[1] Maria Cl
Martin J. Gartland,[9] and Kimb**

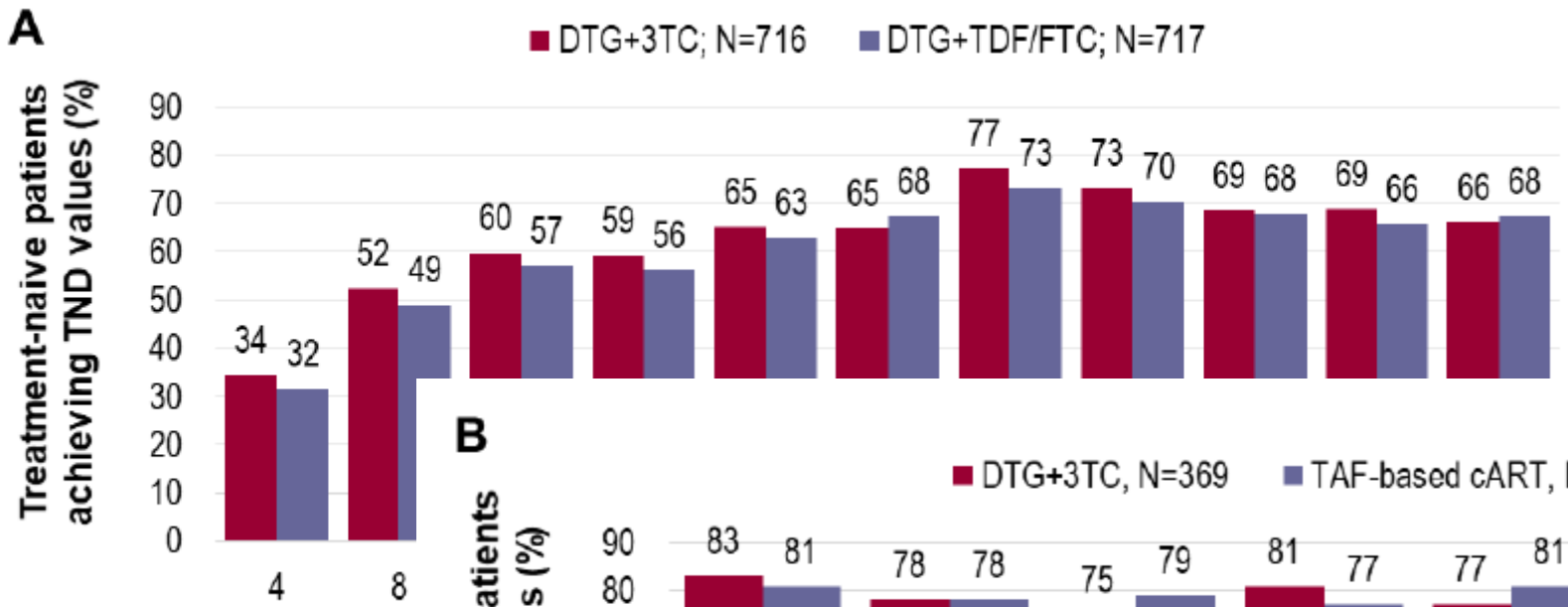
[1]ViiV Healthcare, Brentford, United Ki
de Bruxelles, Brussels, Belgium, [5]Tripl
Montreal, Quebec, Canada, [8]Praxis ar

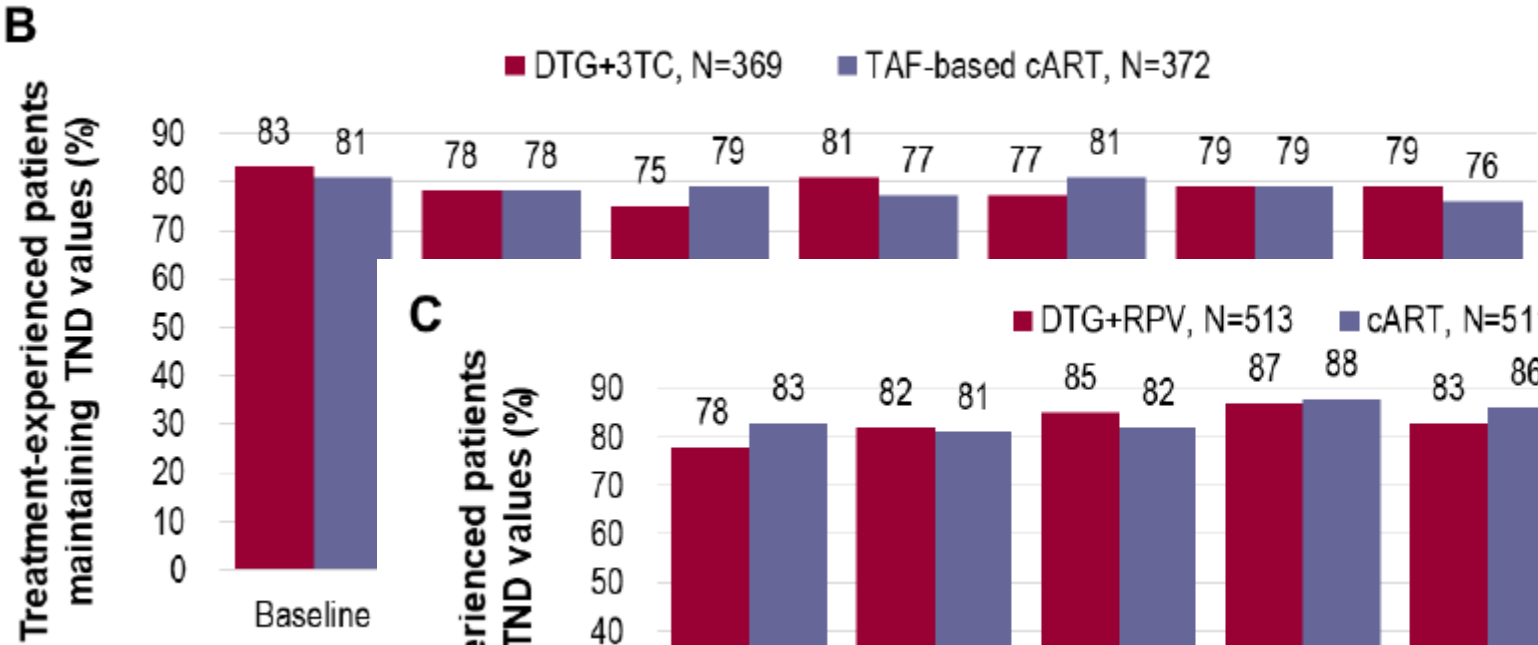
Wynne,[9] Michael Aboud,[1]

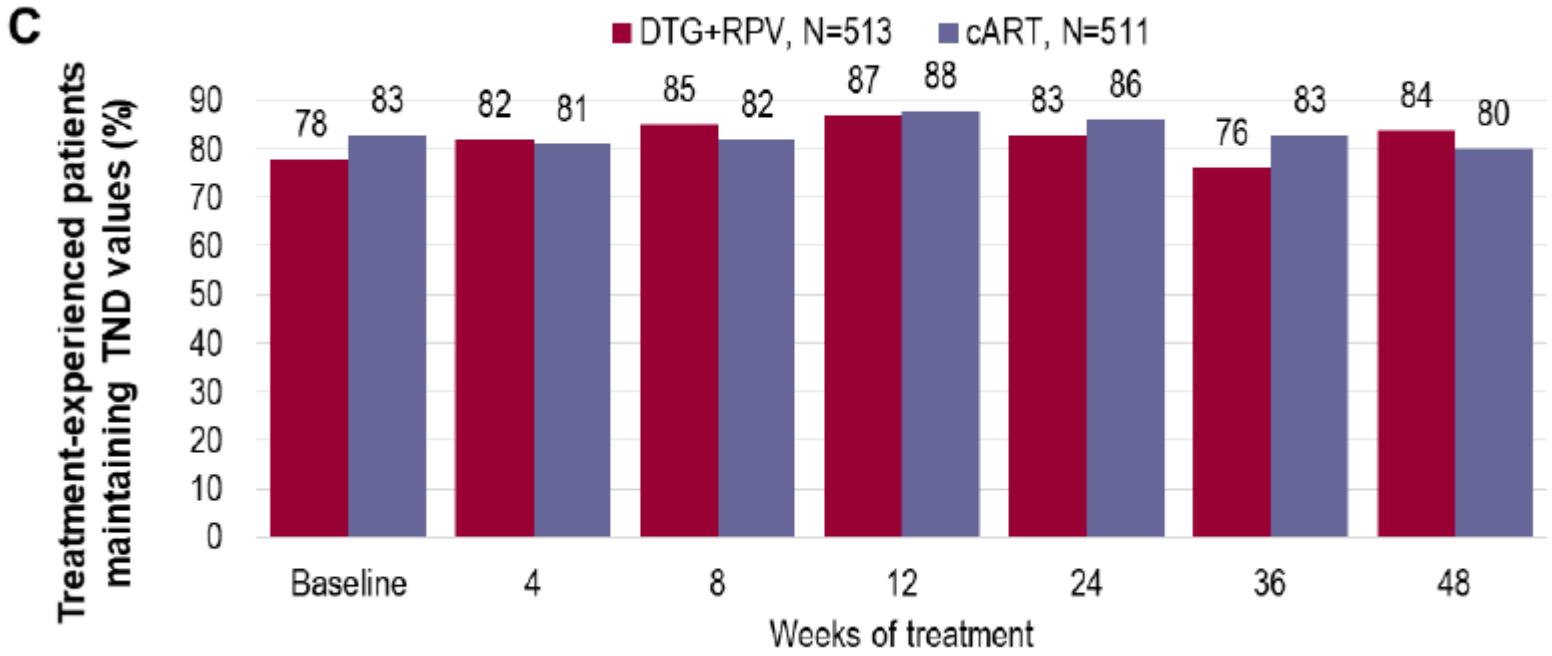
[4]CHU Saint-Pierre, Université Libre
McGill University Health Centre,
ockley Park, United Kingdom


a
0.003
NI
NI
NI
100
90
84
82
84
82
82
84
NI
100
90
80
70
60
50
40
30
20
10
0
Patients with HIV-1 RNA <50 copies/mL at 96-weeks (%)
86
79
89
69
77
86
317/369
294/372
885/990
99/143
103/133
19/22
TANGO [51]
DTG/3TC
TAF-based cART
SWORD 1&2[53]
DTG + RPV early and late switch
SALT[55]
ATV/r + 3TC
ATLAS-M[56]
ATV/r + 3TC
HLS03/2012[57]
DRV/r + 3TC
115/140
128/153
42/63
42/55
19/21
GEMINI-1 & -2[16]
BL HIV-RNA >100,000 copies/mL
DTG+3TC
DTG+TDF/FTC
GEMINI-1 & -2[16]
BL CD4 cell count <200 cells/mL
DTG+3TC
DTG+TDF/FTC
URBAN[15]
DTG/3TC

GEMINI 1,2
1000<CVP<500,000/ml
Pas de résistances majeures
Pas de VHB
Pas de VHC



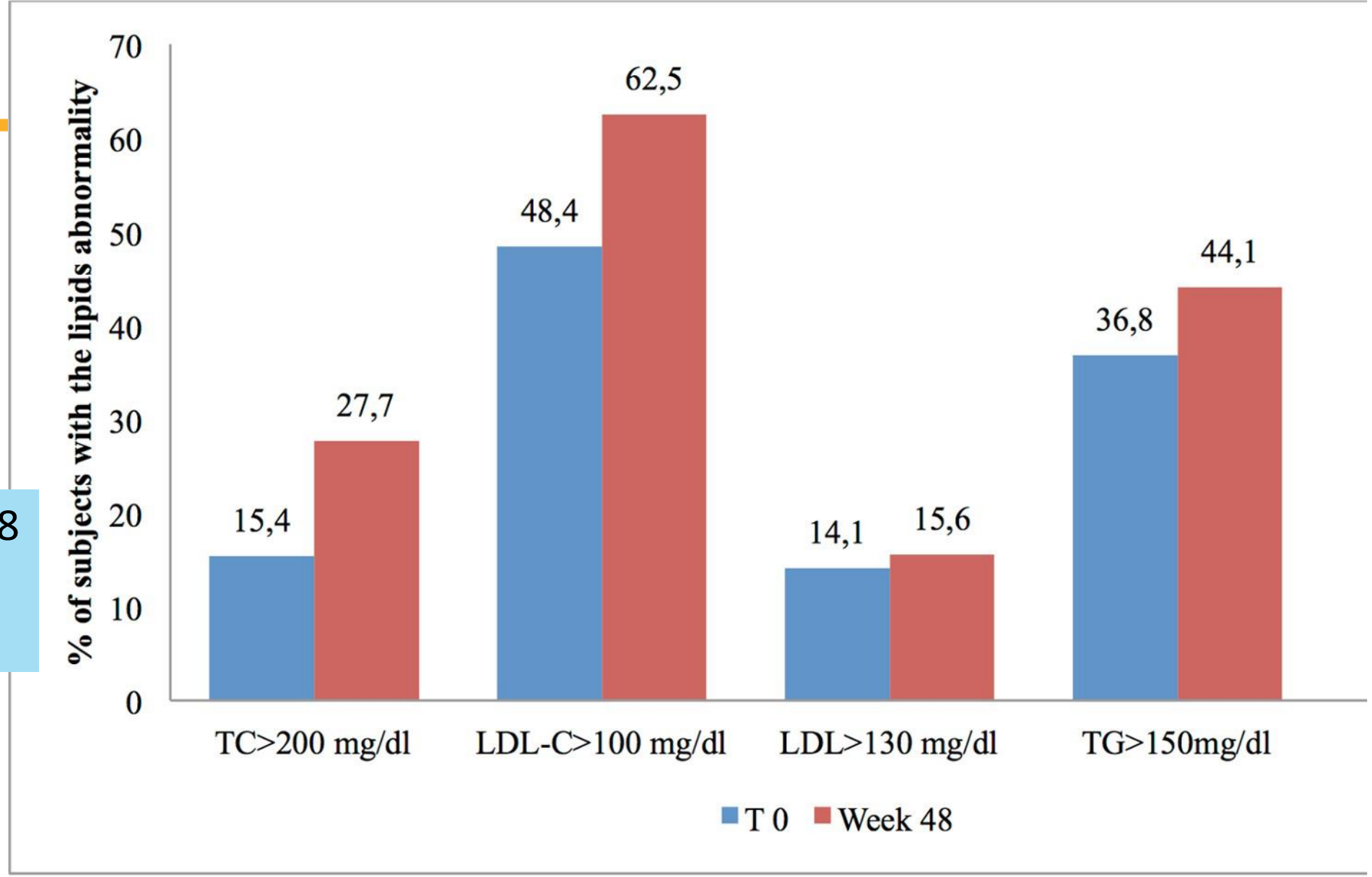




Diagnostics **2021**, *11*, 809. https://doi.org/10.3390/

76 patients
Succès virologique
Allègement
48 semaines

CVP indétectable S48
Protéinurie <
Déminéralisation <



TC – total cholesterol, LDL-C – Low-density lipoprotein cholesterol, TG – triglyceride

p>0.05 for all comparisons

Another option in patients who are virologically suppressed (VL < 50 copies/mL) while receiving a regimen of NNRTI + two NRTIs, and who have never experienced virological failure, is a switch to the two-drug combination of DTG + RPV. Data from two clinical trials (SWORD I and II)[99] show that this regimen maintains virological suppression as a switch strategy in patients who have not previously experienced virological failure. This should not be done in patients who have chronic hepatitis B as TDF and 3TC (or FTC) should always form part of their treatment. Hepatitis B surface antigen status should therefore always be tested before making this switch.

ations for two-drug first-line regimen

gravir + lamivudine

avir + lamivudine was shown to have non-
fficacy to a three-drug regimen in RCTs.[93]
these trials did not include patients with
00 000 copies/mL. Furthermore, virological
ion was lower in patients with a CD4+
200 cells/µL. Therefore, we do not routinely
nd this regimen unless neither TDF nor ABC
ed. Importantly, hepatitis B must be excluded
onsidering this regimen as patients with
B must receive TDF + 3TC (or FTC) to prevent
ergence of 3TC/FTC resistance.

5.11.1.1 Dolutegravir with lamivudine

Recommendations

- We recommend that ART can be switched to dolutegravir with lamivudine in people with virological suppression (Grade 1A) but this regimen is **not** suitable for those:
  - With a history of previous virological failure on an INSTI regimen or anti-retroviral resistance to lamivudine or INSTIs (Grade 1A);
  - With hepatitis B co-infection (Grade 1A);
  - At risk of hepatitis B who are not immune (GPP).

TABLE 1 Preferred and alternative antiretroviral regimens for treatment-naïve adults with HIV.

Regimen	Main requirements	Additional guidance (see footnotes)
Recommended regimens		
Two NRTIs + INSTI		
ABC/3TC + DTG or ABC/3TC/DTG	HLA-B*57:01 negative, HBsAg negative	(I) ABC: HLA-B*57:01, cardiovascular risk, (II) Weight increase (DTG)
TAF/FTC/BIC		(II) Weight increase (BIC, TAF)
TAF/FTC or TDF/XTC + DTG		(II) Weight increase (DTG, TAF), (III) TDF: prodrug types. Renal and bone toxicity. TAF dosing
TAF/FTC or TDF/XTC + RAL qd or bid		(II) Weight increase (RAL, TAF), (III) TDF: prodrug types. Renal and bone toxicity. TAF dosing, (IV) RAL: dosing
One NRTI + INSTI		
XTC + DTG or 3TC/DTG	HBsAg negative, HIV VL <500 000 copies/mL	(II) Weight increase (DTG), (V) Not recommended after PrEP failure
Two NRTIs + NNRTI		
TAF/FTC or TDF/XTC + DOR or TDF/3TC/DOR		(II) Weight increase (TAF), (III) TDF: prodrug types. Renal and bone toxicity. TAF dosing, (VI) DOR: HIV-2

Dual therapies

In persons with suppression of HIV-VL < 50 copies/mL for the past 6 months these dual therapy strategies should only be given if there is

a) no historical resistance and
b) HBV immunity with anti-HBs antibodies (if non-immune provide HBV Vaccination, if isolated HBc antibodies see the section on Treatment and Monitoring of Persons with HBV/HIV Co-infection for details)

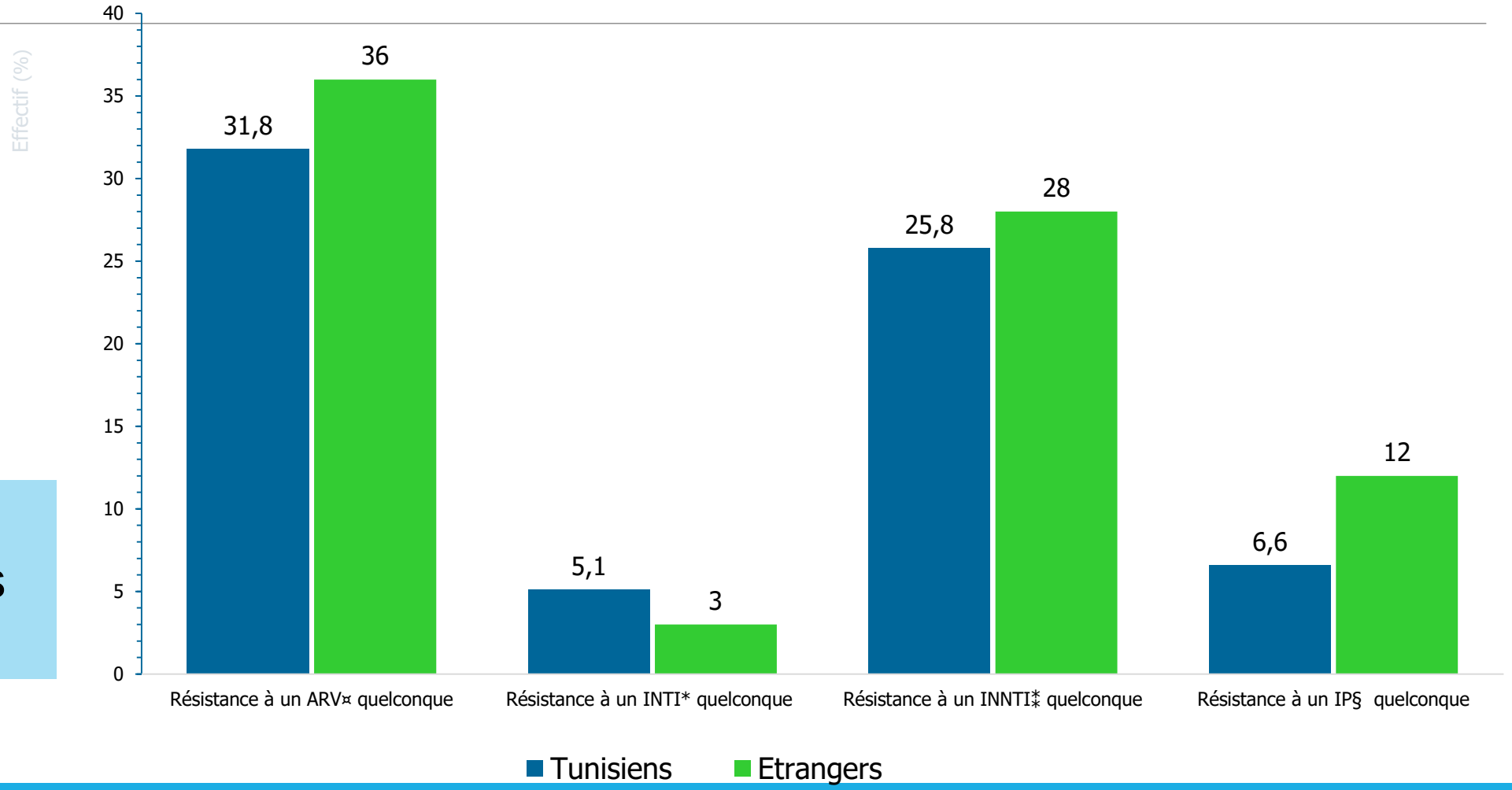
Oral dual therapies supported by large randomized clinical trials or meta-analyses:

DTG + RPV
XTC + DTG
XTC + DRV/b

In clinical trials, these strategies have not been associated with more virological rebounds than triple therapy. There were a few cases of resistance development on DTG + RPV and CAB + RPV

Résistances chez les naïfs en Tunisie

256 patients
198 tunisiens
2012-2022



Résistances aux INTI

Utilisation 3TC +++

	Bas niveau résistance N (%)	Résistance intermédiaire N (%)	Haut niveau de résistance N (%)	Résistance globale N (%)
3TC	2 (0,8)	1 (0,4)	**4 (1,5)**	**7 (2,7)**
ABC	2 (0,8)	5 (1,9)	3 (1,2)	**10 (3,9)**
FTC	1 (0,4)	1 (0,4)	5 (1,5)	7 (2,7)
TFV	5 (1,9)	1 (0,4)	1 (0,4)	7 (2,7)
AZT	3 (1,2)	1 (0,4)	3 (1,2)	7 (2,7)

Houda Limem, thèse 2024

Résistance aux INNTI

Schéma allégé contenant RPV ??

Résistance globale aux INNTI : **26,2%**

Résistance à tous les INNTI : 3,1%

	Bas niveau de résistance N (%)	Résistance intermédiaire N (%)	Haut niveau de résistance N (%)	Résistance globale N (%)
EFV	6 (2,3)	1 (0,4)	**13 (5,1)**	**20 (7,8)**
NVP	13 (5,1)	1 (0,4)	**15 (5,8)**	**29 (11,3)**
ETR	**20 (7,8)**	3 (1,2)	2 (0,8)	**25 (9,8)**
RPV	**43 (16,8)**	1 (0,4)	5 (1,9)	**49 (19,1)**

218 PVVIH

5 ans

Pas d'échec virologique

15 blips < 50 copies/ml

11 décès

Majoration CD4

Long-term dolutegravi virologically

Franco Maggiolo[1*], Roberto
Annapaola Callegaro[4] and

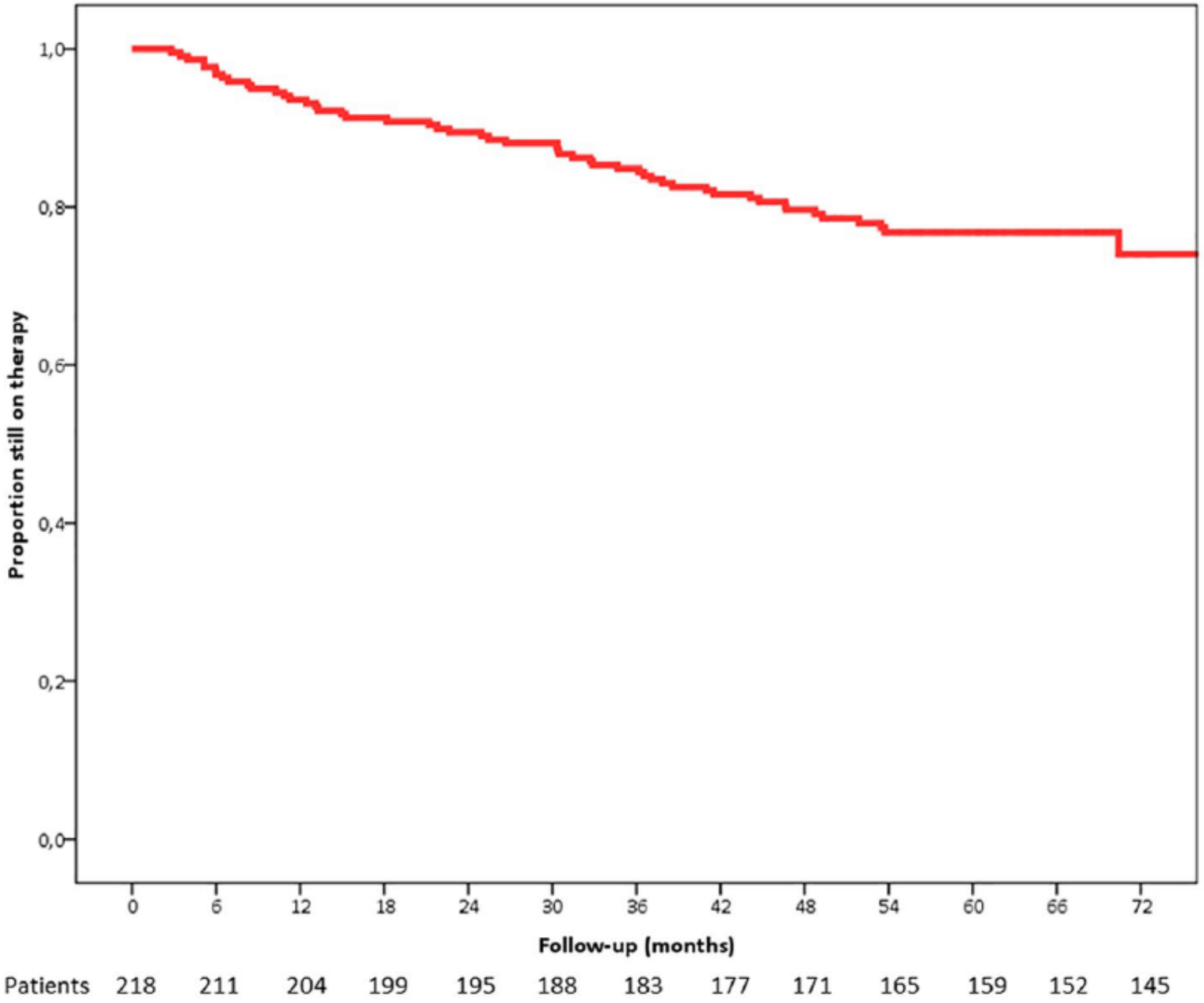


Fig. 1 Kaplan-Meier curve representing the proportion of subjects still on the DTG-3TC combination

Comprimés longue durée d'action

CROI 2024

Essai phase2

52 : un comprimé par jour

BIC/FTC/TAF

52: un comprimé/semaine

Islatavir 2 mg/Lenacapavir 300 mg

S24: 94,2% CVP<50 copies/ml

S48 loading…

March 06, 2024

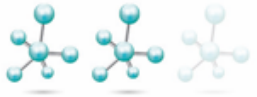
Gilead and Merck Announce Phase 2 Data Showing an Investigational Oral Once-Weekly Combination Regimen of Islatravir and Lenacapavir Maintained Viral Suppression at Week 24

– Week 24 Results Support Continued Development as a Potential Long-Acting Oral Combination Treatment Option in Virologically Suppressed People with HIV –

– Novel Investigational Combination Regimen has the Potential to be the First Oral Weekly HIV Treatment, Helping to Address Unmet Needs –

- Nombre de comprimés

- Nombre de jours



- Un ou deux médicaments

- Injectables longue durée

LATTE
Phase 2b
243 PVVIH
3 résistances
4 effets indésirables
82% CR vs 71% EFV/2INTI

LATTE2
Phase 2b
286 patients
2 résistances
11 EII majeurs
99%

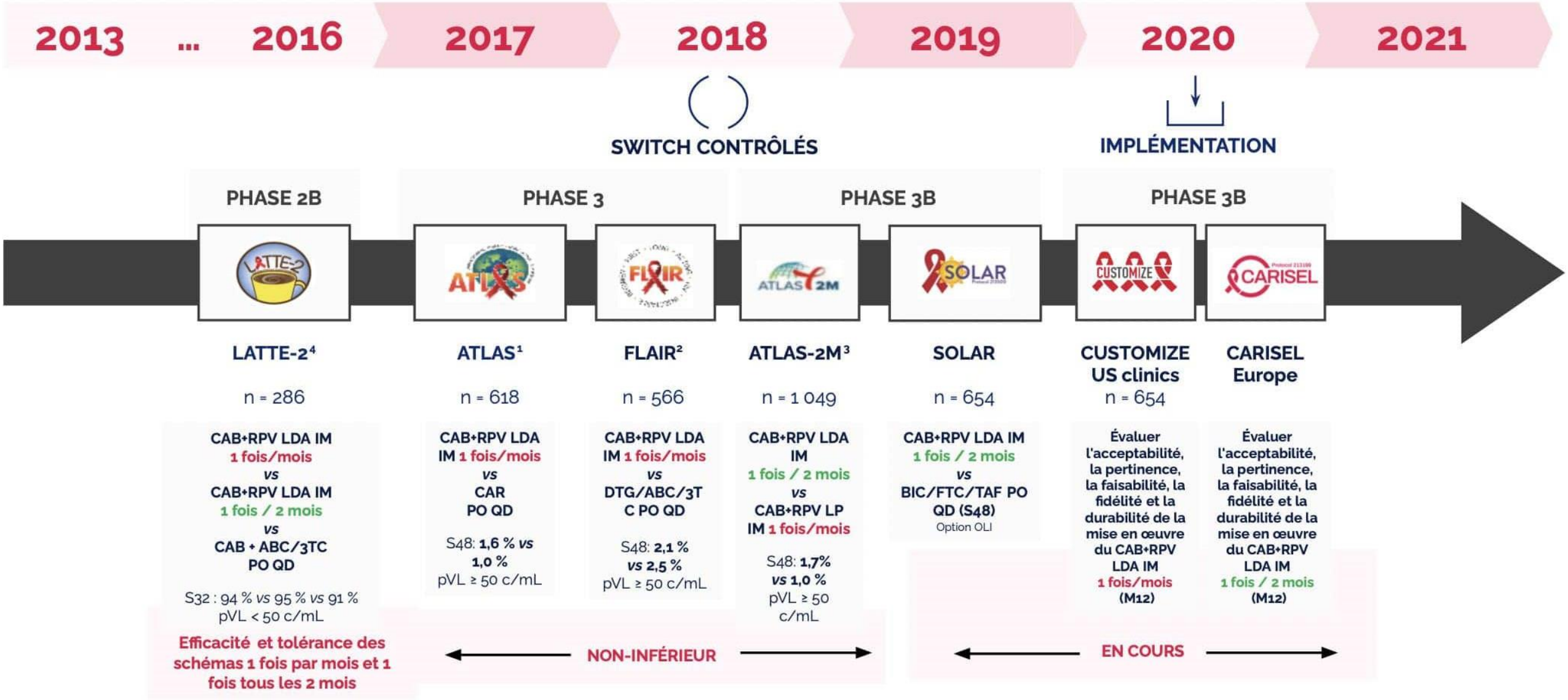
ATLAS
CAB + RPV LA 308
SOC 308
6 résistances
Pas de différence

FLAIR
CAB + RPV LA 278
ABC/3TC/DTG 283
3 résistances
Pas de différence

f long-acting cabotegravir and rilpivirine injectable for the treatment of HIV-1 infected adults.

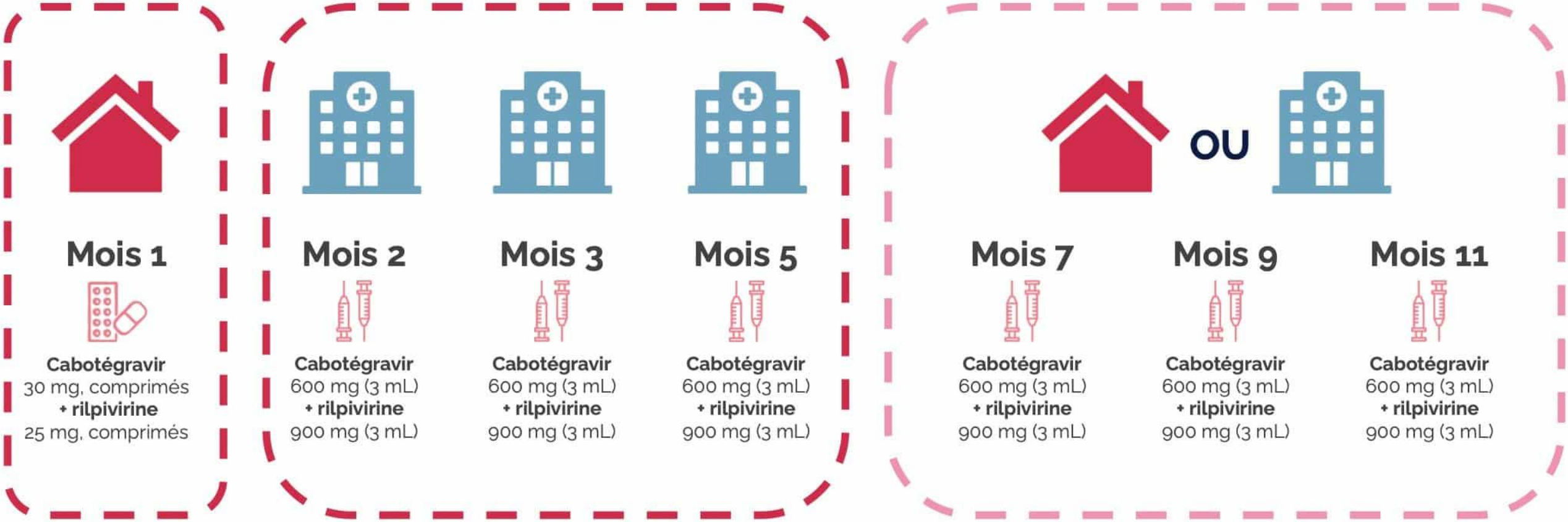
Arms	n	Primary outcome	Result, n (%)	AE leading to discontinuation (maintenance period), n (%)	Treatment-emergent resistance	Differences observed
ng) +RPV (25 mg) aily	60	*Number (%) of participants in the maintenance-exposed population with HIV-1 RNA<50 copies/mL at week 48*	48 (80)	1 (2)	1 patient: RT: E138Q; INSTI: Q148 R 1 patient: RT: K101 K/E, E138E/A 1 patient: RT: K101 K/E, E138E/K	Cabotegravir + rilpivirine groups (82%) vs efavirenz group (71%).
ng) +RPV (25 mg) aily	60		48 (80)	0 (0)	None	
ng) +RPV (25 mg) aily	61		53 (87)	1 (2)	None	
FV (600 mg) once	62		44 (71)	2 (4)	None	
400 mg) + RPV g) q4 w	115	*Number (%) of participants in the maintenance-exposed population with HIV-1 RNA<50 copies/mL at week 96*	100 (87)	8 (7)	None	q8 w LA regimen vs oral therapy: adjusted difference [95%CI], 2.8% [5.8–11.5] q8 w LA regimen vs oral therapy: adjusted difference [95%CI], 3.7% [4.8 – 12.2]
600 mg) + RPV g) q8 w	115		108 (94)	2 (2)	1 patient: RT: K103 N, E138 G, K238 T; INSTI: Q148 R 1 patient: INSTI: R269 R/G	
mg) + ABC/3TC 0 mg) once daily	56		47 (84)	1 (2)	None	
400 mg) + RPV g) q4 w	308	*Number (%) of participants in the maintenance-exposed population with HIV-1 RNA>50 copies/mL at week 48*	5 (1.6)	11 (3.6)	1 patient: RT: E138A/E/K; INSTI: L74I 1 patient: RT: E138A/E/K; INSTI: L74I, N155 H 1 patient: RT: E138A/E/K, V108I	LA regimen vs oral therapy: adjusted difference [95%CI], 0.6%, [−1.2–2.5]
therapy once	308		3 (1.0)	4 (1.3)	1 patient: RT: M184 V, G190 S; INSTI: L74I 1 patient: RT: M184 V 1 patient: RT: M230 M/I	
400 mg) + RPV g) q4 w	278	*Number (%) of participants in the maintenance-exposed population with HIV-1 RNA>50 copies/mL at week 48*	6 (2.1)	8 (2.8)	1 patient: RT: E138 K; INSTI: Q148 R, L74I 1 patient: RT: E138E/A/K/T; INSTI: Q148 R, L74I 1 patient: RT: K101E. INSTI: L74I, G140 R	LA regimen vs. oral therapy: adjusted difference [95%CI]: −0.4%, [−2.8–2.1]
DTG (600/300/) once daily	283		7 (2.5)	2 (0.7)	None	

very 8 weeks. NRTI: nucleoside reverse transcriptase inhibitor. EFV: efavirenz. LA: Long-acting. CAB: cabotegravir. RPV: rilpivirine. SOC: standard of care. RT: retrotranscripase. INSTI: acavir. 3TC: lamivudine. DTG: dolutegravir.
n baseline DNA sequencing undertaken on stored samples in the ATLAS study. All patients presented with virological failure had the L74I mutation on baseline DNA in the FLAIR



1. Swindells S, *et al. N Eng J Med* 2020;382:1112–23; 2. Orkin C, *et al. N Eng J Med* 2020;382:1124–35; 3. Overton E.T. *et al. Lancet* 2020; 396: 1994–2005; 4. Margolis DA *et al. Lancet.* 2017;390:1499-1510

Initiation du traitement à l'hôpital avant le passage en ville



Phase orale optionnelle

We recommend that long-acting cabotegravir/rilpivirine can be used in people who:

- Face challenges taking daily oral ART (GPP) *and*
- Have been virally suppressed to <50 copies/mL for at least 6 months (Grade 1A) *and*
- Have no known or suspected NNRTI or INSTI resistance (Grade 1A) *and*
- Have no history of virological failure or unplanned treatment interruption on NNRTI- or INSTI-containing ART (Grade 1A) *and*
- Have no history of INSTI monotherapy (GPP) *and*
- Can commit to 2-monthly attendance for injections (GPP) *and*
- Accept the risk of virological failure and resistance despite complete adherence and the potential implications for U=U (GPP) *and*
- Have a body mass index (BMI) of <30 kg/m^2 AND non-A1/6 subtype if baseline resistance is unavailable (Grade 1A) *and*
- Do not need a tenofovir containing regimen for the treatment or prevention of hepatitis B (Grade 1A).

Long-acting intramuscular dual therapy CAB + RPV

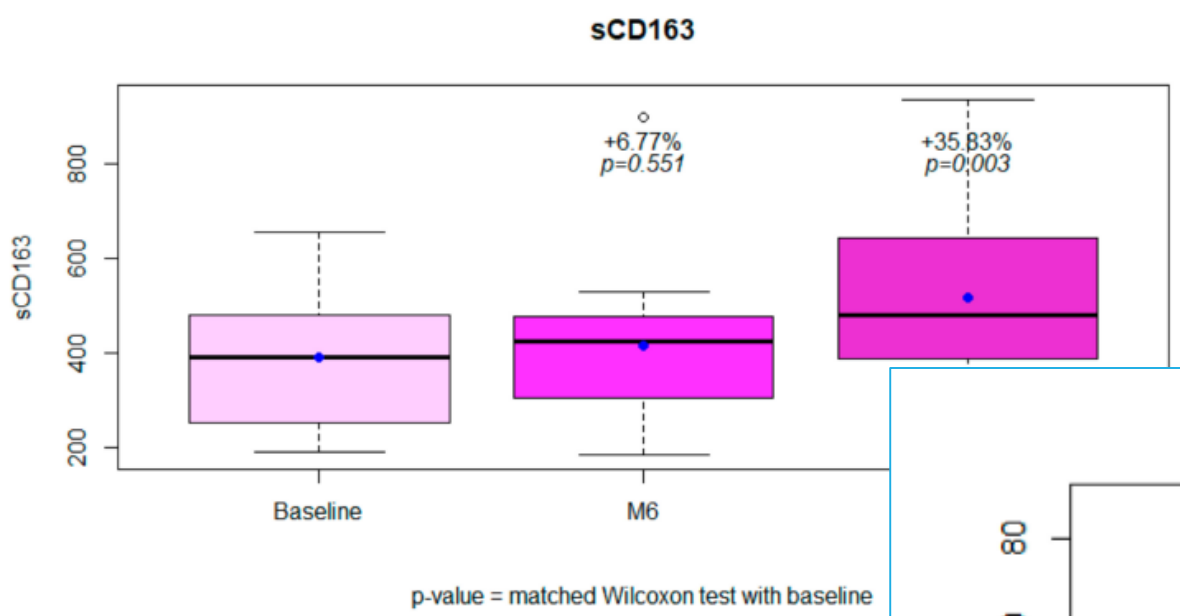
- The use of oral lead-in (1 month) is optional
- Injections are administered every 2 months. In case of bridging, see the section on Drug-Drug Interactions after Oral and Intramuscular Administration of CAB and RPV

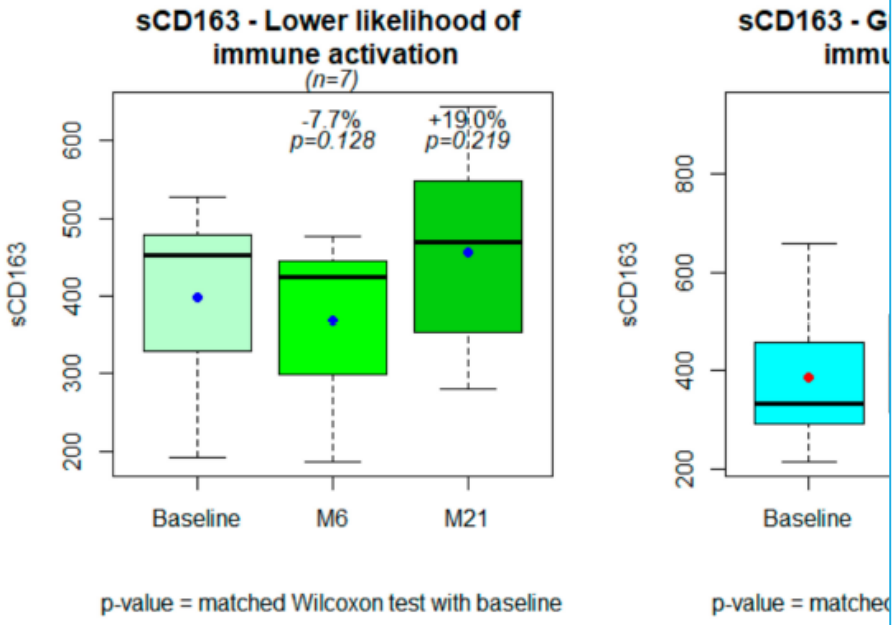
Initiation phase (start on day of last oral pills)	Continuation phase
Day 0: CAB 600 mg/ RPV 900 mg Month 1: CAB 600 mg/ RPV 900 mg	From month 2 onwards: CAB 600 mg/ RPV 900 mg every 2 months

The following baseline factors, when combined, are associated with risk of virologic failure and resistance:

- Archived RPV-associated mutations
- HIV subtype A6/A1
- BMI ≥ 30 kg/m^2

Risque?





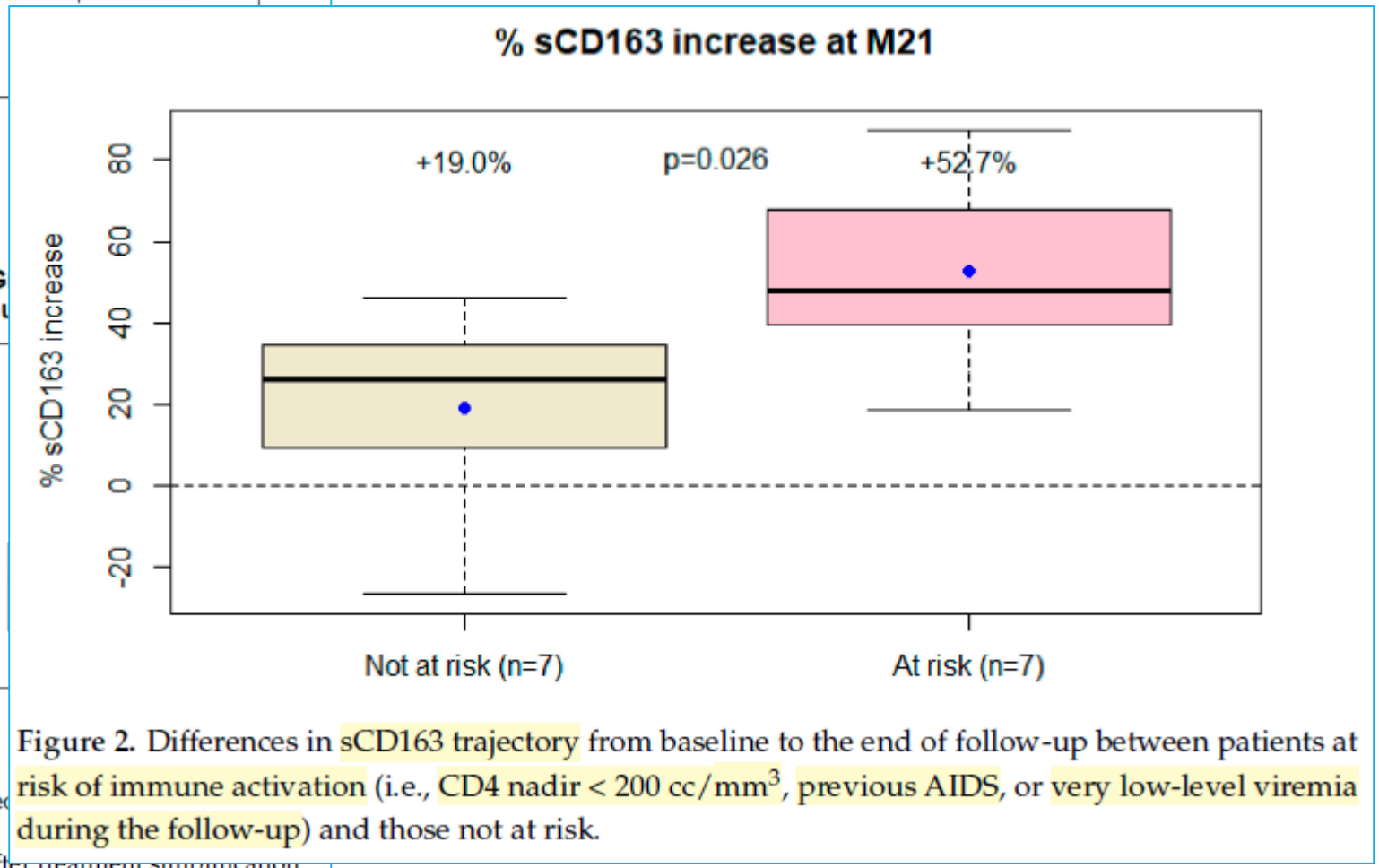


Figure 2. Differences in sCD163 trajectory from baseline to the end of follow-up between patients at risk of immune activation (i.e., CD4 nadir < 200 cc/mm^3, previous AIDS, or very low-level viremia during the follow-up) and those not at risk.

Figure 1. Changes in sCD163 from baseline to 6 months and 21 months after treatment simplification for the entire population (n = 14) and in subjects with lower (n = 7) or greater (n = 7) likelihood of immune activation.

Conclusion

Dogme trithérapie détruit

Nouvelles molécules

- Puissantes
- Haut seuil de mutation
- Demi-vie longue

Possibilité allègement

- Bithérapie orale
- Bithérapie orale longue durée d'action
- Bithérapie injectable longue durée d'action

Conclusion

Respect drastique des indications

Gain de coût sur traitement

Dépenses contrôles >>

Risque reprise inflammation

- Aggravation comorbidités

Réveil sanctuaires?